Gulf War and Health: Volume 7: Long-Term Consequences of Tramautic Brain Injury

Committee on Gulf War and Health: Brain Injury in Veterans and Long-Term Health Outcomes

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Gulf War and Health

Volume 7

Long-Term Consequences of Traumatic Brain Injury

Committee on Gulf War and Health: Brain Injury in Veterans and Long-Term Health Outcomes

Board on Population Health and Public Health Practice

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This report has been reviewed in draft form by persons chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards of objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We thank the following for their review of this report:

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PREFACE

The Institute of Medicine (IOM) has a long-standing role of providing assistance to the Department of Veterans Affairs (VA) with regard to veterans' health. The current series of studies on Gulf War and Health, of which this study is one, began in 1998 when Congress passed two laws on Gulf War veterans' health in response to the recognition that many Gulf War veterans returning from the 1991 Persian Gulf War were suffering from a multisymptom illness of poorly understood pathogenesis that proved difficult to diagnose and treat.

The United States is once again engaged in a military conflict in the Middle East. The conflicts in Afghanistan (Operation Enduring Freedom, OEF) and in Iraq (Operation Iraqi Freedom, OIF) have been characterized by a type of combat different from that seen in the 1991 war, in that there have been many more deaths, polytrauma, and TBI. The VA, under authorization granted in the 1998 legislation, has asked IOM to determine long-term health outcomes associated with traumatic brain injury (TBI). TBI has been called the signature injury of OEF and OIF primarily due to blast exposure that is characteristic of this conflict. Exposure to blast might cause instant death, injuries with immediate manifestation of symptoms, or injuries with delayed manifestation. Blast-induced neurotrauma (BINT), however, has not been studied sufficiently to confirm reports of long-term effects.

That many returning veterans have TBI will likely mean long-term challenges for them and their family members. Veterans will need support systems at home and in their communities to assist them in coping with the long-term sequelae of their injuries. Further, many veterans will have undiagnosed brain injury because not all TBIs have immediately recognized effects or are easily diagnosed with neuroimaging techniques.

In an effort to detail the long term consequences of TBI, the committee read and evaluated some 1,900 studies that made up its literature base, and it developed criteria for inclusion of studies to inform its findings. It is clear that brain injury, whether penetrating or closed, has serious consequences. The committee sought to detail those consequences as clearly as possible and to provide a scientific framework to assist the brave men and women who have fought in OEF and OIF as they return home. We are honored to have been of service.

I am deeply appreciative of the expert work of our committee members and their extraordinary commitment to the task at hand. The committee extends its appreciation to the many people who presented information at its open meeting and to the IOM staff. In particular we would like to thank Renee Wlodarczyk, Jen Saunders, and Naoko Ishibe who helped with a myriad of tasks including literature searches, retrieving articles, entering data into the numerous tables in the document, and for their contributions in the development of several chapters of the report. We appreciate Joe Goodman's attention to our meeting and travel needs; and to Carolyn Fulco for her guidance and oversight.

George W. Rutherford, MD, AM
Chair, Committee on Gulf War and Health: Brain Injury in Veterans and Long-term Health Outcomes

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SUMMARY

The first Persian Gulf War, an offensive led by US and coalition troops in January 1991, followed the August 1990 Iraqi invasion of Kuwait. The war was over on February 28, 1991; an official cease-fire was signed in April 1991, and the last US troops who participated in the ground war returned home on June 13, 1991. In all, about 697,000 US troops had been deployed to the Persian Gulf during the conflict. That war resulted in few injuries and deaths among coalition forces, but returning veterans soon began to report numerous health problems that they believed were associated with their service in the gulf. Those veterans were potentially exposed to numerous biologic and chemical agents, including vaccinations and other prophylactic medications, nerve agents, depleted uranium, pesticides, solvents, and combusted and uncombusted fuels.

On October 7, 2001, the United States began combat operations in Afghanistan in response to the September 11, 2001 terrorist attacks. The war in Afghanistan is often referred to as Operation Enduring Freedom (OEF). In March 2003, the United States became engaged in military operations in Iraq. The Iraq War, referred to as Operation Iraqi Freedom (OIF) or the second Iraq War, and OEF have been fundamentally different from the first Gulf War, not only in the number of troops deployed and in its duration but in the type of warfare and in the numbers of deaths and injuries, particularly brain injuries.

In 1998, in response to the growing concerns of ill Gulf War veterans, Congress passed two laws: PL 105-277, the Persian Gulf War Veterans Act, and PL 105-368, the Veterans Programs Enhancement Act. Those laws directed the secretary of veterans affairs to enter into a contract with the National Academy of Sciences (NAS) to review and evaluate the scientific and medical literature regarding associations between illness and exposure to toxic agents, environmental or wartime hazards, and preventive medicines or vaccines associated with Gulf War service and to consider the NAS conclusions when making decisions about compensation. The study was assigned to the Institute of Medicine (IOM), which has published several volumes, including Gulf War and Health, Volume 1: Depleted Uranium, Pyridostigmine Bromide, Sarin, Vaccines; Gulf War and Health, Volume 2: Insecticides and Solvents; Gulf War and Health, Volume 3: Fuels, Combustion Products, and Propellants; Gulf War and Health: Updated Literature Review of Sarin; and Gulf War and Health, Volume 5: Infectious Diseases.

The legislation did not preclude an IOM recommendation of or a Department of Veterans Affairs (VA) request for additional studies, particularly if a subject of concern arises. Consequently, a VA request that IOM consider whether there is an increased risk of amyotrophic

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lateral sclerosis in all veteran populations resulted in Amyotrophic Lateral Sclerosis in Veterans, a request for an examination of all health effects in veterans deployed to the Persian Gulf irrespective of specific exposures resulted in Gulf War and Health, Volume 4: Health Effects of Serving in the Gulf War, and a request for a review of long-term health effects that might be associated with deployment-related stress resulted in Gulf War and Health, Volume 6: Health Effects of Deployment-Related Stress. The present report is in response to a VA request regarding whether traumatic brain injury has long-term health effects.

TRAUMATIC BRAIN INJURY

Damage to the brain after trauma (for example, a blow or jolt to the head, a penetrating head injury, or exposure to an external energy source) is referred to as traumatic brain injury (TBI). TBI may be open (penetrating) or closed and is categorized as mild, moderate, or severe, depending on the clinical presentation. A brain injury that results from something passing through the skull, such as a bullet discharged from a gun or fragments from a missile, would be referred to as a penetrating or open head injury. A brain injury that results from something hitting the head or from the head hitting something forcefully, such as the dashboard of a car, is referred to as a nonpenetrating or closed head injury. According to the Centers for Disease Control and Prevention, mild TBI is manifested as a brief change in mental status or unconsciousness, whereas severe TBI results in an extended period of unconsciousness or amnesia. According to the World Health Organization Collaborating Task Force on Mild Traumatic Brain Injury, mild TBI might also be referred to as a concussion, a minor brain injury, a mild head injury, or a minor head injury. Furthermore, it has been noted that the term concussion, often used to indicate a mild or moderate brain injury, refers to a disturbance in neurologic function caused by the mechanical force of rapid acceleration or deceleration, and can include varied symptoms and severity.

With regard to determining TBI severity, different methods have been used in the last 3 decades to measure the magnitude of brain damage and to predict its outcome. The mostly widely used tool for measuring severity is the Glasgow Coma Scale (GCS), which was developed in 1974 by Teasdale and Jennett as a measure of neurologic deficits after TBI and was an important contribution to the standardization of early assessment of TBI. It is based on a simple method of scoring three domains—eye-opening, verbal response, and motor function—and yields a total score of 3 (comatose or nonresponsive) to 15 (no deficits in any of the three domains). The interpretation of scores at the ends of the scale is relatively straightforward, but scores like 8 or 9 or 11 or 12 might be subject to judgment error. Although the GCS is relatively straightforward, the classification of severity has been inconsistent. Many incidence studies have classified severity according to GCS scores of 3–8 as severe, 9–12 as moderate, and 13–15 as mild or minor.

Other methods and instruments have been used to determine injury severity, such as the Abbreviated Injury Scale (AIS) and the International Classification of Diseases (ICD). Clinical measures—such as loss of consciousness (LOC), duration of posttraumatic amnesia (PTA), and computed tomography of brain lesions—have also been used to assess TBI severity.

During peacetime, over 7,000 Americans with a TBI diagnosis are admitted to military and veterans hospitals each year. During the Vietnam War, 12–14% of all combat casualties had a TBI, and another 2–4% had a TBI plus a lethal wound of the chest or abdomen. In the recent

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conflicts in Afghanistan and Iraq, however, TBI appears to account for about 22% of casualties. All patients admitted to Walter Reed Army Medical Center in the period January 2003–February 2005 who had been exposed to blasts were routinely evaluated for brain injury, and 59% of them were found to have TBI. Of those injuries, 56% were moderate or severe, and 44% were mild. In many people who sustain mild TBI, the effects might not be immediately evident and might not be evident with conventional neuroimaging. That clearly presents a problem for VA with regard to preparation for the return of veterans from OEF and OIF with TBI that might not be apparent.

OPERATION ENDURING FREEDOM AND OPERATION IRAQI FREEDOM

Throughout OEF and OIF, explosive devices have become more powerful, their detonation systems more creative, and their additives more devastating. According to the Department of Defense (DOD) Personnel and Procurement Statistics, 75% of all US military casualties in OEF and OIF are caused by explosive weaponry. As of January 2008, DOD reported that over 5,500 soldiers had suffered TBIs. As a continuing threat to our troops, blast injury, especially blast-induced neurotrauma (BINT), has been called the signature wound of the war in Iraq. In both civilian and military environments, exposure to a blast might cause instant death, injuries with immediate manifestation of symptoms, or injuries with delayed manifestation. BINT is a complex type of TBI that features closed (blunt) head injury that may be accompanied by polytrauma. The pathobiology of BINT parallels that seen in TBI, including secondary injury cascades that result in vasogenic and cytotoxic edema, emerging hemorrhagic lesions, metabolic disturbances, compromise of neural and glial structures that leads to cell death, and diffuse axonal injury in cases of sudden brain acceleration and deceleration.

As of June 30, 2008, there had been about 1.64 million US deployments as part of OEF and OIF and 4128 US troop fatalities. The ratio of wounded troops to troop fatalities, 7.37:1, is higher than that in previous military conflicts, probably because of the widespread use of body armor, improved battlefield medical response, and advances in aeromedical evacuation. Despite those improvements, military personnel continue to be critically wounded, and TBI continues to be a source of concern. Furthermore, there is an outdated dogma that neurologic impairments caused by primary blasts are rare because the skull provides excellent protection for the brain, that is, that brain injury is a consequence solely of air emboli in cerebral blood vessels. Despite recent clinical findings, experimental findings, and experience in contemporary military operations that suggest that substantial short-term and long-term neurologic deficits can be caused by blast exposure without a direct blow to the head, the old belief prevails in the professional literature and in civilian clinical practice. Indeed, information on blast injuries consists mainly of the consequences of secondary and tertiary blast mechanisms. Although BINT is one cause of in-theater injuries, it is often underdiagnosed. Its complex clinical syndrome is caused by the combination of all blast effects. It is noteworthy that blast injuries are usually manifested in a form of polytrauma, that is, injury involving multiple organs or organ systems.

CHARGE TO THE COMMITTEE

The charge to this IOM committee was to examine the strength of the evidence of an association between TBI and long-term health effects. The committee also was to consider the severity of TBI (that is, mild, moderate, and severe) and possible long-term consequences.

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COMMITTEE'S APPROACH TO ITS CHARGE

The committee began its work by overseeing extensive searches of the peer-reviewed medical and scientific literature, including published articles, other peer-reviewed reports, and dissertations. The searches retrieved over 30,000 potentially useful epidemiologic studies, and their titles and abstracts were reviewed. The committee focused its attention on clinical and epidemiologic studies of adults with long-term health effects that resulted from TBI by any mechanism, such as occupational injury, motor-vehicle collision, sports injury, gunshot wound, or other act of violence, including military combat. Studies of patients with TBI due to malignancy, stroke, infection, ischemia, other diseases or disorders of the brain, intoxication, or oxygen deprivation were not considered. The committee did not systematically review studies of young children, the elderly, or brain-injured patients in litigation for compensation claims. Its review excluded case reports, case series with few participants, and studies of acute outcomes that resolved within days to a few months (that is, less than 6 months). The committee did not review general studies of "disability" as a gross measure of morbidity but rather evaluated studies that associated TBI with specific health outcomes.

After its assessment of the 30,000 titles and abstracts, the committee members identified about 1,900 studies for further review. Those studies were objectively evaluated without preconceived ideas about health outcomes or the existence or absence of associations. The committee adopted a policy of using only peer-reviewed published literature or unpublished reports that had undergone rigorous peer review, such as dissertations and some government reports, as the basis of its conclusions. The process of peer review by fellow professionals increases the likelihood of high quality but does not guarantee the validity of a study or the ability to generalize its findings. Accordingly, committee members read each study critically and considered its relevance and quality. They did not collect original data, nor did they perform any secondary data analysis.

LIMITATIONS OF THE STUDIES OF TRAUMATIC BRAIN INJURY

Many of the studies reviewed by the committee presented substantial obstacles to determining associations between TBI and long-term health outcomes in that they were beset by limitations that are commonly encountered in epidemiologic studies, including lack of a representative sample, selection bias, lack of control for potential confounding factors, self-reporting of exposure and health outcomes, unknown premorbid status, and outcome misclassification.

Some of the studies reviewed did not specify the time between injury and followup, so the committee could not determine whether the outcome lasted longer than 6 months. Many studies involved populations in rehabilitation centers where subjects might have had multiple injuries that included TBI but the initial TBI might have been due to a stroke or a brain tumor; these studies presented several problems, such as lack of representativeness of the younger veteran population and an inherent selection bias, for example, if they included only people who had health insurance.

Most cohort studies rely on self-reporting of symptoms on questionnaires. Symptom self-reporting potentially introduces reporting or recall bias, which occurs when the group being

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studied reports what it remembers more frequently than a comparison group does. Reporting bias can lead to overestimation of the prevalence of symptoms or diagnoses in the TBI population. Symptom self-reporting might sometimes introduce another type of bias known as outcome misclassification, which leads to errors in how symptoms are classified into outcomes and analyzed.

Apart from some large population-based studies of mortality after TBI and a few others of neurologic outcomes, many of the studies evaluated by the committee had small samples. When a study sample is too small, it is possible to miss clinically important differences; this phenomenon is known in epidemiology as type II error. In such studies, attempts to examine even smaller subpopulations magnify the difficulties and reduce the likelihood of detecting meaningful differences. Of the studies examined by the committee, those with small samples were also sometimes hampered by other problems, including low participation rate, loss to followup, inadequate duration of followup, and self-reporting of symptoms.

An additional limitation of the studies reviewed is the lack of uniformity in defining the severity of TBI. Studies typically note whether the injury was a penetrating or a closed head injury but often used different criteria to assess severity. The committee found it difficult to compare outcomes among studies, particularly in the “moderate” TBI category, because researchers used different durations of loss of consciousness and of posttraumatic amnesia to define severity. Similarly, the range of scores on the GCS was not always uniformly applied in defining mild, moderate, and severe TBI.

The committee focused on studies of people who had sustained TBI, followed the subjects to determine long-term sequelae, and generally asked whether a specific outcome was more likely in people with TBI than in controls without TBI. The committee discussed characteristics of the optimal control group for such studies because the type of controls could influence inferences drawn from the studies examined. When the outcome was a medical condition or a social outcome, the committee considered the best comparison group to be made up of people who had other traumatic injuries but without TBI (such as bone fractures) and were in the same facility as the subjects with TBI; such controls permit examination of the effects of TBI on outcome independently of the general effects of trauma and of the common risk factors that lead to trauma. When the outcome studied was death, the committee agreed that comparison with age- and sex-specific mortality in the general population provided the best comparison.

The committee found many studies for inclusion in its review. However, many excellent studies were excluded because they were not designed to answer the question posed to the committee, that is, What are the long-term outcomes associated with sustaining TBI?

OVERVIEW OF HEALTH OUTCOMES

It is clear that TBI can have detrimental effects on a person, whether it is mild, moderate, or severe. The committee found many instances of long-term outcomes of TBI, although some acute outcomes resolved or lessened over time (such as some neurocognitive and psychosocial dysfunction) whereas other sequelae became more apparent several years after injury (such as psychiatric outcomes). Many studies found a dose–response relationship with regard to TBI severity and outcome: generally, the more severe the TBI, the more severe the outcome. For example, with regard to neurocognitive outcomes, the committee found sufficient evidence of an

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association between penetrating TBI and decline in neurocognitive function associated with the region of the brain affected and the volume of brain tissue lost. That evidence was consistently found in veterans of World War II and Vietnam. With regard to closed head injuries, the committee found sufficient evidence of an association between severe TBI and neurocognitive deficits, limited but suggestive evidence of an association between moderate TBI and neurocognitive deficits, and inadequate and insufficient evidence of an association between mild TBI and neurocognitive deficits.

With regard to neurologic effects, the studies reviewed had numerous findings, including a strong association between brain injury and unprovoked seizures. For example, there is a causal association between penetrating TBI or severe closed TBI and unprovoked seizures, whereas the risk of unprovoked seizures after mild TBI is limited but suggestive of an association. In general, the risk of seizures after all types of TBI severity appears to be highest in the first year after trauma and declines thereafter. Some of the literature reviewed supports an association between TBI and neurodegenerative diseases—for example, studies that demonstrated a sufficient association between moderate or severe TBI and dementia of the Alzheimer type or parkinsonism, although sufficient evidence of an association with dementia pugilistica could be supported only in professional boxers. Other studies reviewed did not support a relationship between TBI and multiple sclerosis or amyotrophic lateral sclerosis and were categorized as inadequate and insufficient to determine whether an association exists. There were endocrine outcomes, such as sufficient evidence of an association between moderate to severe TBI and growth hormone insufficiency and hypopituitarism, however, the studies only supported a finding of limited and suggestive evidence of an association between moderate to severe TBI and diabetes insipidus.

Psychiatric outcomes have been discussed by the committee, and there is some uncertainty regarding the mechanisms linking TBI and psychiatric diagnoses. For example, it is not clear whether psychopathologic conditions after TBI are biologic consequences of the injury, reactions to the person's cognitive and social dysfunction after TBI, or a continuation of pre-existing conditions. The committee has chosen, however, to use the terminology of primary psychiatric disorders, as has been the custom in the TBI literature. The committee notes that the predominance of studies indicated that groups with TBI (mild, moderate, or severe) had higher rates of major depression 6 months or more after TBI than did appropriate comparison groups. The committee concluded that there is sufficient evidence of an association between TBI and depression and aggressive behaviors. The association between mild TBI and posttraumatic stress disorder (PTSD) appears to be different between military and civilian populations. Studies conducted in military personnel who served in the Gulf War led the committee to conclude that there is limited but suggestive evidence of an association between TBI and PTSD. In contrast, studies conducted in civilian populations led the committee to conclude that there is inadequate and insufficient evidence to determine whether an association exists between TBI and PTSD. With regard to aggressive behaviors, the studies support a conclusion of sufficient evidence of an association, but TBI is not associated with increased drug and alcohol use as there is limited but suggestive evidence of an association between TBI and decreased alcohol and drug use. Finally, the literature supported a finding of limited but suggestive evidence of an association between moderate to severe TBI and psychoses generally appearing in the second and third years after TBI.

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Social functioning is often severely hampered after TBI, especially if it is severe. Social function in those hospitalized with TBI is adversely affected, relative to those with no injury, for at least 1 year. Results of some studies suggest that difficulties might continue up to 15 years after injury, depending on TBI severity. TBI decreases the probability of postinjury employment in people who were workers before they were injured, lengthens the time it takes them to return to work (if they do return), and decreases the likelihood that they will return to the same positions. Those adverse effects are related to the severity of injury as measured with neurologic severity indicators and are related even more strongly to post-TBI neuropsychologic impairment. Penetrating head injury sustained in wartime clearly is associated with unemployment. The probability of being employed 15 years after the Vietnam War was related to the number of residual neurologic deficits, brain-volume loss, and cognitive status. TBI also adversely affects leisure and recreation, social relationships, functional status, quality of life, and independent living. By 1 year after injury, psychosocial problems appear to be greater than problems in basic activities of daily living. The committee concluded that there was sufficient evidence of an association between penetrating TBI and long-term unemployment and between moderate to severe TBI and long-term adverse social-function outcomes, particularly unemployment and diminished social relationships. With regard to mild TBI, however, the committee concluded that the evidence was inadequate and insufficient with respect to long-term adverse social functioning, including unemployment, diminished social relationships, and decrease in the ability to live independently.

There is sufficient evidence of a causal relationship between injury and premature death in people who survive penetrating head injury. There is inadequate and insufficient evidence to determine whether an association exists between mild, moderate, or severe TBI and premature death in people who survive 6 months or longer after TBI. That is largely because of the paucity of studies. Finally, in the subset of patients with moderate or severe TBI either admitted into or discharged from rehabilitation centers or those receiving disability support, there is sufficient evidence of an association between TBI and premature death; however, that finding is limited to patients who have sustained injuries severe enough to warrant inpatient rehabilitation or disability support.

Large population-based registry studies of brain cancer found no association between TBI and brain tumors, but there is evidence from some other studies of a weak but significant association between TBI and meningioma and of an increase in risk of brain tumors 10 years or more after TBI; that suggests a long latent period before clinical presentation. The committee believes that the possibility of an association between TBI and brain tumors is not a closed question and that longer-term followup, especially with large registry-based studies, is warranted to determine whether there is a measurable increase in risk and, if so, when it is most likely to be observed. For now, the committee concludes that the inconsistent results among the studies are most supportive of a classification of inadequate and insufficient evidence to determine whether an association exists.

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RECOMMENDATIONS

Scoring of Severity of Blast Induced Neurotrauma

BINT is a complex type of TBI that features closed (blunt) head injury that may be accompanied by a penetrating brain injury. The pathobiology of BINT parallels that of TBI. Because moderate, moderate to severe, and severe blast-induced neurotrauma (BINT) is often part of complex polytrauma, proper diagnosis of BINT should include both classification of blast injuries and scoring of the severity of head injury. The most recent version of the AIS incorporates blast injuries and is regularly used by the US Army; it can be used for global scoring of all injuries. In hospitals, the modified Pathology Scoring System can yield additional information that might be valuable in designing treatment strategies and predicting outcomes. A combination of the head AIS, as an anatomic measure, and the GCS, as a physiologic measure of brain-injury severity, is useful in initial estimation of brain damage. Nevertheless, use of additional TBI scoring systems is recommended, especially in the case of mild TBI or suspected concussion or when medical records provide less detailed information about the injury and its circumstances. In the military environment, use of the Brief Traumatic Brain Injury Screen and the Military Acute Concussion Evaluation is recommended for every soldier who has a history of blast exposure (even low-intensity blast exposure).

The committee recommends that the Department of Defense use the Brief Traumatic Brain Injury Screen and the Military Acute Concussion Evaluation for every soldier who has a history of blast exposure (even of low-intensity blast exposure).

Experimental and Clinical Studies of Blast Induced Neurotrauma

Blast injury, especially BINT, is a continuing threat to our troops. In both civilian and military environments, exposure to a blast might cause instant death, injuries with immediate manifestation of symptoms, or injuries with delayed manifestation. There is a paucity of information in the scientific literature regarding the sequelae of blast injury, and there is a need for prospective, longitudinal studies to confirm reports of long-term effects of exposure to blasts. Because of lack of information, adverse neurologic and behavioral changes in blast victims might be underestimated, and valuable time for preventive therapy or timely rehabilitation might be lost.

The committee recommends that the Department of Defense and the Department of Veterans Affairs support prospective, longitudinal studies to confirm reports of long-term or latent effects of exposure to blasts. Those studies should examine the consequences of blast-induced neurotrauma, recovery timeline, and any factors that improve or worsen outcomes.

Additionally, animal models provide the framework for predicting outcomes and developing optimal therapeutics for BINT; however, after reviewing the literature, the committee came to the conclusion that there is a need for more refined animal models of BINT. They should be aligned with emerging data on the human response to BINT. The accessibility to acute clinical data on human BINT from DOD and VA is essential for refining the animal models.

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The committee recommends that the Department of Defense and the Department of Veterans Affairs support research on animal models of blast-induced neurotrauma. Consideration should be given to developing models that would be relevant to human traumatic brain injury that encompass a more comprehensive experimental design. That could include studies that measure both behavior and pathology that might differ by traumatic brain injury severity. It would be important for the Department of Defense and the Department of Veterans Affairs to work with the research community and provide acute clinical data on human blast-induced neurotrauma to enable refinement of the animal models.

Registry Control Groups

The studies of TBI evaluated by the committee had numerous limitations. A primary limitation results from the nature of the control or comparison group assembled by the investigator. In an attempt to improve the quality of future TBI studies, the committee has described what it considers to be appropriate control groups.

Evaluating whether TBI in service members is associated with particular outcomes requires comparison groups of service members who have experienced injuries other than TBI and service members who have been deployed but not injured. Comparing outcomes of TBI with outcomes in those reference groups is the only means of identifying which outcomes are due solely to TBI and not to deployment or to injury in general.

The committee recommends that the Department of Veterans Affairs include, in the development of the Traumatic Brain Injury Veterans Health Registry (hereafter referred to as "the registry"), other service members who could provide a valid comparison for the analysis of outcomes. Comparison groups should be made up of injured persons without traumatic brain injury or blast exposure, uninjured deployed veterans, and uninjured nondeployed but previously active-duty veterans. Those groups could be compared with persons who have received a diagnosis of traumatic brain injury and with those who have possible or probable traumatic brain injury. The three comparison groups should have samples large enough to provide reference rates of outcomes of interest. Furthermore, the registry needs to be representative of the traumatic brain injury population to be able to determine associations between such injury and various outcomes. There should be no exclusions on the basis of sex, race, geographic region, or rank.

Access to medical records is essential to ensure the validity of a recommended research design. Neurologic status, computed tomographic or magnetic resonance imaging, electroencephalography, associated nonbrain injuries, and durations of impaired consciousness and PTA amnesia are important for the accurate classification of service members into appropriate groups.

For the registry to have the greatest benefit, predeployment information on all groups mentioned above should be made available to the injury-research community. Complete medical information on outcomes of each person (stripped of personal identifiers) in the registry should be available whether or not care is sought at or covered by the VA system.

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Predeployment and Postdeployment Testing

In considering the question of long-term outcomes of TBI, questions arise that are very seldom addressable in current studies: What was the predeployment cognitive ability of the person? How did the TBI affect the baseline functioning? The answers to those questions are important in isolating and understanding the effects of TBI itself on long-term outcome. Most information about TBI effects comes from studies of World War I, World War II, and Vietnam veterans, but those studies are based on penetrating or severe closed head injuries. In the current conflict, many injuries are related to blast, and outcomes are unknown.

In an effort to understand the long-term outcomes of traumatic brain injury, including consequences that might be related to blast, the committee recommends that *all* deployed military personnel undergo predeployment neurocognitive testing. The committee also recommends postdeployment neurocognitive testing of representative samples of military personnel (including those with traumatic brain injury, those with other non-TBI injuries, and uninjured service members without blast exposure).

Among service members with predeployment and postdeployment testing, it should be possible to link the results for each person with DOD and VA records, and those should be made available for research and treatment.

SUMMARY OF FINDINGS

The committee attempted to express its judgment on the available data clearly and precisely. It agreed to use the categories of association (see below) that have been established and used by previous Committees on Gulf War and Health and other IOM committees that have evaluated vaccine safety, effects of herbicides used in Vietnam, and indoor pollutants related to asthma. The categories of association have gained wide acceptance over more than a decade by Congress, government agencies (particularly VA), researchers, and veterans groups.

The five categories of association sound a recurring theme: the validity of an association is likely to vary to the extent to which common sources of spurious associations can be ruled out as reasons for the observed association. Accordingly, the criteria for each category express a degree of confidence based on the extent to which sources of error have been reduced. In each case below, findings are described for penetrating TBI or for closed TBI generally indicated as mild, moderate, or severe.

Sufficient Evidence of a Causal Relationship

Evidence is sufficient to conclude that there is a causal relationship between TBI and a specific health outcome in humans. The evidence fulfills the criteria of sufficient evidence of an association and satisfies several of the criteria used to assess causality, such as strength of association, dose–response relationship, consistency of association, temporal relationship, specificity of association, and biologic plausibility.

- Penetrating TBI and unprovoked seizures.
- Penetrating TBI and premature death.

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- Severe or moderate TBI and unprovoked seizures.

Sufficient Evidence of an Association

Evidence is sufficient to conclude that there is a positive association; that is, a consistent association has been observed between TBI and a specific health outcome in human studies in which chance and bias, including confounding, could be ruled out with reasonable confidence as an explanation for the observed association.

- Penetrating TBI and decline in neurocognitive function associated with the region of the brain affected and the volume of brain tissue lost.
- Penetrating TBI and long-term unemployment.
- Severe TBI and neurocognitive deficits.
- Moderate or severe TBI and dementia of the Alzheimer type.
- Moderate or severe TBI and parkinsonism
- Moderate or severe TBI and endocrine dysfunction, particularly hypopituitarism.
- Moderate or severe TBI and growth hormone insufficiency
- Moderate to severe TBI and long-term adverse social-function outcomes, particularly unemployment and diminished social relationships.
- Moderate or severe TBI, in the subset of patients who are either admitted into or discharged from rehabilitation centers or receive disability support, and premature death.
- TBI and depression.
- TBI and aggressive behaviors.
- TBI and postconcussion symptoms (such as memory problems, dizziness, and irritability).
- Professional boxing and dementia pugilistica.

Limited/Suggestive Evidence of an Association

Evidence is suggestive of an association between TBI and a specific health outcome in human studies but is limited because chance, bias, and confounding could not be ruled out with reasonable confidence.

- Moderate or severe TBI and diabetes insipidus.
- Moderate or severe TBI and psychosis.
- Moderate TBI and neurocognitive deficits.
- Mild TBI resulting in loss of consciousness or amnesia and unprovoked seizures.
- Mild TBI and ocular and visual motor deterioration.
- Mild TBI with loss of consciousness and dementia of the Alzheimer type.
- Mild TBI with loss of consciousness and parkinsonism.
- Mild TBI and posttraumatic stress disorder in Gulf War military populations.
- TBI and decreased alcohol and drug use in the 1–3 years after injury
- TBI and completed suicide.

Inadequate/Insufficient Evidence to Determine Whether an Association Exists

Evidence is of insufficient quantity, quality, consistency, or statistical power to permit a conclusion regarding the existence of an association between TBI and a specific health outcome in humans.

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- Moderate or severe TBI and brain tumor.
- Mild, moderate, or severe TBI that is survived for 6 months or more and premature death.
- Mild TBI and neurocognitive deficits.
- Mild TBI (without loss of consciousness) and dementia of the Alzheimer type.
- Mild TBI and posttraumatic stress disorder in civilian populations.
- Mild TBI and long-term adverse social functioning, including unemployment, diminished social relationships, and decrease in the ability to live independently.
- TBI and mania or bipolar disorder.
- TBI and attempted suicide.
- TBI and multiple sclerosis.
- TBI and amyotrophic lateral sclerosis.

Limited/Suggestive Evidence of *No* Association

Evidence from several adequate studies, covering the full range of severity of TBI that humans are known to encounter, is consistent in not showing a positive association between TBI and a specific health outcome. A conclusion of no association is inevitably limited to the conditions, magnitudes of exposure (types of TBI—mild, moderate, and severe or penetrating), and length of observation in the available studies. The possibility of a very small increase in risk of the health outcome after TBI cannot be excluded.

- None

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INTRODUCTION

The first Persian Gulf War, an offensive led by US and coalition troops in January 1991, followed the August 1990 Iraqi invasion of Kuwait. The war was over on February 28, 1991; an official cease-fire was signed in April 1991, and the last US troops who participated in the ground war returned home on June 13, 1991. In all, about 697,000 US troops had been deployed to the Persian Gulf during the conflict. That war resulted in few injuries and deaths among coalition forces, but returning veterans soon began to report numerous health problems that they believed were associated with their service in the gulf. Those veterans were potentially exposed to numerous biologic and chemical agents, including vaccinations and other prophylactic medications, nerve agents, depleted uranium, pesticides, solvents, and combusted and uncombusted fuels.

On October 7, 2001, the United States began combat operations in Afghanistan in response to the September 11, 2001, terrorist attacks. The war in Afghanistan is often referred to as Operation Enduring Freedom (OEF). In March 2003, the United States became engaged in military operations in Iraq. The Iraq War, referred to as Operation Iraqi Freedom (OIF) or the second Iraq War, and OEF have been fundamentally different from the first Gulf War, not only in the number of troops deployed and in its duration but in the type of warfare and in the numbers of deaths and injuries, particularly brain injuries.

BACKGROUND

In 1998, in response to the growing concerns of ill Gulf War veterans, Congress passed two laws: PL 105-277, the Persian Gulf War Veterans Act, and PL 105-368, the Veterans Programs Enhancement Act. Those laws directed the secretary of veterans affairs to enter into a contract with the National Academy of Sciences (NAS) to review and evaluate the scientific and medical literature regarding associations between illness and exposure to toxic agents, environmental or wartime hazards, and preventive medicines or vaccines associated with Gulf War service and to consider the NAS conclusions when making decisions about compensation. The study was assigned to the Institute of Medicine (IOM), and to date several volumes have been published including:*Gulf War and Health, Volume 1: Depleted Uranium, Pyridostigmine Bromide, Sarin, Vaccines*(IOM, 2000); *Gulf War and Health, Volume 2: Insecticides and Solvents* (IOM, 2003); *Gulf War and Health, Volume 3: Fuels, Combustion Products, and Propellants* (IOM, 2005); *Gulf War and Health: Updated Literature Review of Sarin* (IOM, 2004); *Gulf War and Health, Volume 5: Infectious Diseases* (IOM, 2006c).

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The legislation did not preclude an IOM recommendation of or a Department of Veterans Affairs (VA) request for additional studies, particularly if a subject of concern arises. Consequently, a VA request that IOM consider whether there is an increased risk of amyotrophic lateral sclerosis in all veteran populations resulted in *Amyotrophic Lateral Sclerosis in Veterans* (IOM, 2006a), a request for an examination of all health effects in veterans deployed to the Persian Gulf irrespective of specific exposures resulted in *Gulf War and Health, Volume 4: Health Effects of Serving in the Gulf War* (IOM, 2006b), and a request for a review of long-term health effects that might be associated with deployment-related stress resulted in *Gulf War and Health, Volume 6: Health Effects of Deployment-Related Stress* (IOM, 2007). The present report is in response to a VA request regarding whether traumatic brain injury has long-term health effects.

TRAUMATIC BRAIN INJURY

Damage to the brain after trauma (for example, a blow or jolt to the head, a penetrating head injury, or exposure to an external energy source) is referred to as traumatic brain injury (TBI). A TBI may be open (penetrating) or closed and is categorized as mild, moderate, or severe, depending on the clinical presentation (Gennarelli and Graham, 2005). The terms mild, moderate and severe TBI are defined and discussed in Chapters 2 and 3.A brain injury that results from something passing through the skull, such as a bullet discharged from a gun or fragments from a missile, would be referred to as a penetrating or open head injury. A brain injury that results from something hitting the head or the head hitting something forcefully, such as the dashboard of a car, is referred to as a nonpenetrating or closed head injury. According to the Centers for Disease Control and Prevention (CDC), a mild TBI is manifest as a brief change in mental status or unconsciousness, whereas a severe TBI results in an extended period of unconsciousness or amnesia (NCIPC, 2008). According to the World Health Organization Collaborating Task Force on Mild Traumatic Brain Injury, a mild TBI also might be referred to as a concussion, a minor brain injury, a mild head injury, or a minor head injury (von Holst and Cassidy, 2004). Furthermore, von Holst and Cassidy (2004) note that the term *concussion* is often used to indicate a mild or moderate brain injury, refers to a disturbance in neurologic function caused by "the mechanical force of rapid acceleration and deceleration", and can cover varied symptoms and severity (see Chapter 2).

Assessment of injury severity is important in the clinical diagnosis and management of patients with TBI. The Glasgow Coma Scale (GCS) has been the gold standard of neurologic assessment of trauma patients since its development by Teasdale and Jennett in 1974. Other TBI severity-classification systems grade single indicators, such as loss of consciousness (LOC) and duration of posttraumatic amnesia (PTA).

During peacetime, over 7,000 Americans with a TBI diagnosis are admitted to military and veterans hospitals each year. During the Vietnam War, 12–14% of all combat casualties had a TBI, and another 2–4% had a TBI and a lethal wound to the chest or abdomen (Okie, 2005). In the recent conflicts in Afghanistan and Iraq, however, TBI appears to account for a larger percentage of casualties, about 22%. Furthermore, all patients admitted to Walter Reed Army Medical Center in the period January 2003–February 2005 who had been exposed to blasts were routinely evaluated for brain injury, and 59% of them were found to have a TBI. Of those injuries, 56% were moderate or severe, and 44% were mild (Okie, 2005). However, for many

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people who sustain a mild TBI, the effects might not be immediately evident and might not be evident with conventional neuroimaging (Gordon et al., 1998). That clearly presents a problem for VA with regard to preparation for the return of veterans from OEF and OIF with a TBI that might not be apparent.

OPERATION ENDURING FREEDOM AND OPERATION IRAQI FREEDOM

According to the Department of Defense (DoD) Personnel and Procurement Statistics, 75% of all US military casualties in OEF and OIF are caused by explosive weaponry (DMDC, 2008). As of January 2008, DoD reported that over 5,500 soldiers had suffered TBIs (CRS, 2008).

As of July 30, 2008, there had been about 1.64 million US deployments as part of OEF and OIF and 4,128 US troop fatalities. The fatalities were due to IEDs (1,683, or 40.8%), car bombs (133, or 3.2%), mortars and rockets (126, or 3.1%), rocket-propelled grenades (102, or 2.5%), and helicopter losses and other hostile and nonhostile causes (2082, or 50.5%) (O'Hanlon and Campbell, 2008).

The ratio of wounded troops to troop fatalities, 7.37:1, is higher than that in previous military conflicts, probably because of the widespread use of body armor, improved battlefield medical response, and advances in aeromedical evacuation (US Congress, House of Representatives, Committee on Veterans' Affairs, 2007). Despite those improvements, military personnel continue to be critically wounded, and TBI continues to be a source of concern.

CHARGE TO THE COMMITTEE

The charge to this IOM committee was to examine the strength of the evidence of an association between TBI and potential long-term health effects. The committee also was to consider the different types of TBI and their possible long-term consequences.

SCOPE OF THE REPORT

The committee was charged with conducting a review of the scientific literature on the association between TBI and long-term health effects. The review included all relevant studies of human TBI in any population (occupational, clinical, and other) caused by any mechanism (for example, motor-vehicle collisions, falls, sports injuries, and gun shots) and long-term health outcomes. Thus, the committee reviewed all papers that provided information about TBI and long-term health outcomes. By examining the full array of evidence of health outcomes in different populations, the committee answered the question, Can sustaining a TBI be associated with a specific health outcome? It should be remembered that an association between a TBI and a health outcome does not mean that all cases of the outcome are related to the TBI; such direct correspondence is the exception rather than the rule in studies of health outcomes in large populations (IOM, 1994).

The committee reviewed more than 30,000 titles and abstracts of scientific and medical articles related to TBI and health outcomes. The committee reviewed the full text of more than

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1,900 peer-reviewed journal articles, many of which are described in this report. Currently, there are no published studies from the Millennium Cohort Study that specifically assess TBI and subsequent health effects. The Millennium Cohort Study which began in 2001 is a DOD-sponsored project that was organized to follow the long-term health of service members for up to 20 years. As a long-term project, the Millennium Cohort Study will likely produce results for TBI-related outcomes in several years.

The details of the committee's approach to its charge, the literature-search strategy, the types of studies that were reviewed, the committee's inclusion criteria, and categories of association are described in Chapter 4.

The committee did not try to determine the costs associated with sustaining a TBI, with acute treatment for TBI, or likelihood of long-term rehabilitation of people with TBI. Nor did it draw conclusions about the long-term treatment of people with a TBI. Those issues were outside the boundaries of its charge. The committee did not review general studies of "disability" as a gross measure of morbidity but rather evaluated studies that associated TBI with specific health outcomes.

ORGANIZATION OF THE REPORT

Chapter 2 reviews the biology of TBI and provides information on the biomechanics and pathophysiology of TBI. Chapter 3 details the epidemiology of adult TBI and discusses the definitions of TBI, and scales and scoring systems used to describe TBI. Chapter 4 provides information regarding the committee's approach to its charge and includes a discussion of how the committee identified and evaluated the literature. Chapter 5 provides an overview of the major cohort studies reviewed by the committee. Chapters 6-10 detail the health outcomes that might be associated with TBI and the committee's conclusions regarding them. Finally, Chapter 11 summarizes the committee's conclusions and provides recommendations.

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2

BIOLOGY OF TRAUMATIC BRAIN INJURY

This chapter presents a general overview of the pathobiology of traumatic brain injury (TBI) and describes two traditional classifications of TBI that are based on findings in animal models and in brain-injured patients. It also addresses the emerging field of blast-induced neurotrauma (BINT) with an emphasis on the biomechanics and physics of injury, pathobiology, and their implications in the context of medical treatment.

PATHOBIOLOGY OF TRAUMATIC BRAIN INJURY

Damage to the traumatized brain is a consequence of the initial mechanical insult and the subsequent activation of secondary pathogenic cascades that collectively influence the temporal progression of the primary insult (McIntosh, 1994; Werner and Engelhard, 2007). It is important to emphasize that human TBI is a heterogeneous disorder in which pathogenic factors may have variable magnitude and occur in various combinations (Graham et al., 2000; Faden, 2002). Single isolated lesions are relatively uncommon in human TBI (Graham et al., 2000). The more common presentation is one of multiple lesions—an outcome that probably reflects injury severity (Graham et al., 2000).

A more generalized picture has emerged from studies of the injured human brain and in animal models of TBI in which the pathobiology of TBI is considered in the context of four phases (described below) (Graham et al., 2002). That categorization has provided a context for better understanding the relationship between the primary insult and secondary pathogenic events. However, the temporal sequence of events may overlap substantially (Moppett, 2007).

Phase 1 represents the initial mechanical damage that results in rupture of cellular and vascular membranes, release of intracellular contents, and cessation of blood flow (McIntosh, 1994; Werner and Engelhard, 2007). Impairment of cerebral blood flow and metabolism leads to anaerobic glycolysis and accumulation of lactic acid (Werner and Engelhard, 2007). Energy-dependent membrane ion pumps fail as adenosine triphosphate (ATP) stores become depleted (Werner and Engelhard, 2007). This phase is governed by the nature of the injury and the profile of the host (Graham et al., 2002). The location and magnitude of brain damage reflect the characteristics of the primary insult; for example, gunshot wounds and vehicular collisions produce different patterns of injury. Specifics of the host—including age, health, sex, and genetics—influence the outcome of the primary insult (Moppett, 2007).

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Phase 2 involves the progressive deterioration of the neural axis that arises from biochemical and molecular events that collectively promote necrotic and apoptotic cell death (Graham et al., 2002; Thompson et al., 2005). The events include release of the excitatory amino acid neurotransmitters, such as glutamate and aspartate; activation of glutamate receptors; influx of calcium into cells and release of calcium from intracellular stores; free-radical generation; and inflammation (Graham et al., 2002; Thompson et al., 2005; Werner and Engelhard, 2007).

In both animal and human studies, TBI results in increased extracellular glutamate concentrations (Schouten, 2007). The increase has been attributed to disruption of the blood-brain barrier and exposure of the brain to humoral-derived glutamate, excessive synaptic release, and decreased glutamate transporter (Yi and Hazell, 2006). Glutamate is the most abundant excitatory neurotransmitter in the brain. In the setting of TBI, an increase in glutamate results in overstimulation of ion-channel–linked and G-protein–linked glutamate receptors. Excessive activation of those ion channels results in prolonged depolarization and ionic imbalance, depletion of ATP stores, and increases in intracellular free calcium that potentially activate numerous pathogenic cascades (Yi and Hazell, 2006).

Intracellular calcium increases rapidly after TBI. That is attributed to an increased influx of Ca^{2+} from the extracellular compartment and a release of Ca^{2+} from intracellular stores, including mitochondria. The increase in intracellular Ca^{2+} leads to activation of intracellular proteases, including calcium-activated neutral proteases (calpains), phospholipases, and endonucleases. Those downstream events mediate cytoskeletal damage, increase intracellular concentrations of free fatty acids, promote free-radical generation, and lead to cell injury and death (Marklund et al., 2006; Werner and Engelhard, 2007).

An important component of the secondary injury cascade results from the generation of reactive oxygen species (ROSs) that include superoxides, hydrogen peroxide, hydroxyl radicals, nitric oxide, and peroxynitrite. Each ROS has an unpaired electron in its outer electron shell and thus is highly reactive and unstable (Calabrese et al., 2008). The excessive production of ROSs is due in part to excitotoxicity, free iron, and interactions between ROSs (Potts et al., 2006). Glutamate-mediated excitotoxicity leads to an increase in intracellular calcium and the subsequent induction of enzymes, such as nitric oxide synthase and xanthine oxidase, that produce free radicals. Mitochondria, when exposed to increased intracellular calcium, become sources of ROSs (Bayir and Kagan, 2008; Sullivan et al., 2005). Accumulation of free iron, resulting from the degradation of heme, catalyzes the formation of superoxide from free oxygen and of the hydroxyl radical from hydrogen peroxide. It is important to note that free radicals such as superoxide and nitric oxide interact with one another to produce other free radicals, including peroxynitrite.

Under physiologic conditions, endogenous antioxidants—including superoxide dismutase, glutathione peroxidase, and catalase—prevent oxidative damage (Potts et al., 2006). Superoxide dismutase catalyzes the conversion of superoxide to hydrogen peroxide, which is further degraded by glutathione peroxidase and catalase to molecular oxygen and water. Low-molecular-weight antioxidants—including glutathione, melatonin, and uric acid—and dietary sources of tocopherols, ascorbic acid and lipoic acid, are also available in the brain.

A group of genes, referred to as vitagenes, function to preserve cellular homeostasis during stress. This family consists of the heat-shock proteins HO-1 and Hsp32. HO-1 confers protection by degrading the pro-oxidant heme and producing biliverdin, the precursor of the

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antioxidant bilirubin. Hsp70 inhibits NFκB signaling and intrinsic apoptotic pathways (Calabrese et al., 2008). In the setting of TBI, each of those neuroprotective systems in the brain becomes overwhelmed, and cell damage arises from free-radical–mediated lipid peroxidation. protein and DNA oxidation, and inhibition of the mitochondrial electron-transport chain.

In general, an inflammatory response in the brain differs from that in other organs. It is exemplified by a more modest and delayed recruitment of leukocytes into the brain than into peripheral organs (Lucas et al., 2006). Brain microglia, in contrast, are activated and release inflammatory mediators beginning within minutes to hours after TBI (Lucas et al., 2006). The mediators often express neurotoxic and neuroprotective properties (Morganti-Kossmann et al., 2007). For example, cytokines may either promote damage or support recovery processes; in some cases, cytokines, such as interleukin-6, may perform both functions (Morganti-Kossmann et al., 2007).

Collectively, the pathogenic cascade of events described in the preceding paragraphs culminates in death of neurons and glia and white matter degeneration. Distinct anatomic patterns of cell death that accompany TBI are evident in neuronal and glial populations and reflect both apoptosis and necrosis (Raghupathi, 2004; Bramlett and Dietrich, 2007). Necrotic death and apoptotic cell death of neurons and glia have been identified in contused areas, the tissue bordering a contusion, and subcortical regions, including the hippocampus, cerebellum, and thalamus (Raghupathi et al., 2000; Raghupathi, 2004; Yakovlev and Faden, 2004). In the case of the contused cortex, gross loss of neurons culminates in a distinct lesion, enlarges with time postinjury, and coincides with progressive atrophy of gray and white matter (Bramlett and Dietrich, 2007).

The vulnerability of astrocytes to TBI has also been recently reconsidered (Floyd and Lyeth, 2007). Historically, the dogma has been that astrocytes are more resistant to injury than neurons (Lukaszevicz et al., 2002). Beyond the characteristic swelling that is seen (Castejon, 1998), those cells show an early injury response that coincides with regional patterns of neuronal vulnerability. Kinetic studies suggest that loss of astrocytes precedes neuronal injury suggesting that early impairment of astrocytes contributes to neuronal death (Floyd and Lyeth, 2007).

Astrocytes play time-dependent diverse roles in TBI (Chen and Swanson, 2003); here we consider their involvement in the acutely injured brain (modulation of extracellular glutamate and K^+ concentrations, scavenging of ROSs, and inflammation) and during wound healing (glial scar formation, restoration of the blood–brain barrier, and growth factor production) (Chen and Swanson, 2003).

Neurons depend on astrocytes for their survival in an acutely injured brain (Chen and Swanson, 2003). After brain injury, glutamate is cleared from the extracellular space by Na^+-dependent glutamate transporters that are localized on astrocytes. Thus, astrocytes are thought to play a critical role in maintaining extracellular glutamate concentrations below toxic levels. Glutamate transport occurs across a steep concentration gradient with much higher concentrations (1–10 mM) in neurons and glia and lower concentrations (less than 10 mM) in the extracellular compartment. That gradient is overcome by the coupling of the intracellular influx of glutamate ions to the inward movement of 3 Na^+ ions and 1 H^+ ion and the outward movement of 1 K^+, a process that shifts energy expenditure from neurons to astrocytes. Glutamate transporters can move substrate both inward and outward.

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Astrocytes can scavenge ROSs, limiting the rise in extracellular K^+, and are active participants in the proinflammatory response (Chen and Swanson, 2003). Astrocytes express higher levels of the antioxidant glutathione than neurons and thus may support neuronal survival. As brain tissue becomes ischemic, extracellular K^+ increases, and this leads to cell swelling and glutamate release. Astrocytes can also limit the increase in intracellular K^+ both indirectly and directly. The former occurs by passive movement of K^+ from the extracellular space into astrocytes that is facilitated by electric coupling between glia. With more K^+, K^+ is actively taken up by the action of astrocyte Na^+/K^+ ATPase.

Finally, there are parallels between the astrocyte response to injury and the proinflammatory response seen in tissues outside the central nervous system. Astrocytes are sources of inducible nitric oxidase synthase and produce cytokines, interleukins, and interferons. The consequences of production of those factors are not completely understood, in part because of their cross-talk with one another and the context of their involvement, which is probably cell-specific.

In the more chronically injured brain, astrocytes are integral to both adverse and beneficial wound-healing events (Chen and Swanson, 2003). They form a glial scar that represents both physical and chemical barriers to axonal regeneration. Counter to that adverse role, reactive astrocytes also participate in the re-establishment of the blood–brain barrier and release trophic factors that may foster plasticity.

Damage to white matter fiber tracts is also a hallmark of TBI. White matter injury is evidenced in part by axonal degeneration, oligodendrocyte death, and demyelination. White matter damage in relative isolation ("pure" diffuse axonal injury) is sufficient to result in severe and persistent morbidity. White matter damage is also often found in combination with other injuries, such as contusion (as produced in many experimental models).

With the advent of imaging, including diffusion-tensor imaging (DTI), evolving white matter damage can be measured in detail and validated against more conventional anatomic outcomes. This approach is exemplified in a recent study that used DTI to assess axonal injury over time (MacDonald et al., 2007). Pericontusional white matter damage was evident in both the acute and subacute periods after experimental TBI. DTI revealed the stereotypic response of early axonal injury followed by demyelination and edema at later periods postinjury. Those findings provide a foundation for translation to the clinical setting where findings in the animal model can be tested for their predictability in human TBI.

Diffuse axonal injury is triggered by acceleration–deceleration forces (Buki and Povlishock, 2006). Although instantaneous direct damage to axons may result from shear and tensile forces, the more common presentation is one whereby axons undergo an evolving process (Maxwell et al., 1997) that begins with focal axolemmal permeability, which permits influx of calcium that is normally excluded by the axon (Buki and Povlishock, 2006) . In vitro studies of fine, unmyelinated fibers also suggest that deformation of axons induces sodium influx via Na^+ channels, which triggers an increase in intra-axonal calcium via the opening of voltage-gated calcium channels and reversal of the Na^+–$Ca2^+$ exchanger (Wolf et al., 2001).

Calcium-induced proteolytic pathways are key components of evolving axonal pathogenesis (Buki and Povlishock, 2006). Calcium-induced activation of the cysteine protease calpain results in degradation of spectrin, a major constituent of the subaxonal cytoskeleton. Calcium-mediated spectrin proteolysis is evident on the surface of mitochondria, and it is

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possible this proteolysis mediates mitochondrial damage. Mitochondrial damage can lead to energy failure and thus disrupt ionic homeostasis, activation of the caspase death cascade, and ultimately structural proteolysis and axonal disconnection.

Cell death is the downstream consequence of perturbations that begin within minutes after injury and extend over a period of days and in some cases months. The kinetics of cell death varies according to cell type, location, nature of the initial insult, and the collective profile of secondary pathogenic events. The mechanisms of cell death, necrosis and apoptosis have been studied in detail. Necrotic cell death involves membrane failure, disruption of ion homeostasis, and rapid degradation of the cytoskeleton (Povlishock and Katz, 2005). In classical light microscopy, neurons initially appear swollen with pyknotic nuclei (Povlishock and Katz, 2005) and show an affinity for histochemical markers of cell injury, including acid fuchsin (Cortez et al., 1989) and fluorojade (Hallam et al., 2004). The nucleus and cytoplasmic organelles, including mitochondria, are swollen; there is cytoplasmic vacuolation; and the integrity of the plasma membrane is compromised (Dietrich et al., 1994; Raghupathi et al., 2000).

The pathobiology of apoptotic cell death has yet to be clearly elucidated. In contrast with necrosis, apoptosis is not linked to disruption of the cell membrane. Rather, the classic picture of an apoptotic neuron includes an intact membrane with internucleosomal DNA strand breaks, nuclear shrinkage, chromatin compaction, and cytoplasmic condensation and disintegration. The end stage of apoptosis is characterized by blebbing of the cell membrane and the emergence of spherical bodies. In contrast with the rapid death seen in necrosis, apoptotic cell death occurs over a longer period. Data also show that apoptosis is associated with a shift in the balance between proapoptotic and antiapoptotic factors (Raghupathi, 2004). Apoptosis has been linked to the excitatory amino acid cascade, increased intracellular calcium, and free radicals (Raghupathi, 2004). Data also show that apoptosis is associated with a shift in the balance between proapoptotic and antiapoptotic factors (Raghupathi, 2004).

Neuronal apoptosis occurs by two pathways: one involves the activation of caspases, and a second is caspase-independent and involves the release of apoptotic factors from mitochondria (Zhang et al., 2005a). Proteolytic cleavage of substrates by caspases, whether by an extrinsic or intrinsic pathway, produces the characteristic phenotype of apoptosis. Some mitochondrial proteins, such as apoptosis-inducing factor (AIF), can induce apoptosis in the absence of activation of caspases. AIF-mediated cell death has been demonstrated in an experimental model of TBI (Zhang et al., 2005a).

The secondary mechanisms occurring during phase 2 are potential targets for therapeutic intervention because of their kinetic profiles (Marklund et al., 2006). They are typically delayed in onset and may extend for hours or months after TBI (Graham et al., 2002; Thompson et al., 2005; Marklund et al., 2006). A key challenge, however, is to translate findings from animal models of TBI to the head-injured patient. Animal models are designed to produce a relatively homogeneous type of injury whereas a key feature of human TBI is heterogeneity. That distinction may partially account for differences in the kinetics of secondary pathogenic events when one compares findings in the animal model with the human condition. For example, with few exceptions, increased extracellular glutamate returns to control values within the first several hours after experimental TBI (Marklund et al., 2006). In contrast, microdialysis data from human TBI have demonstrated an increase in glutamate that is sustained for up to 9 days after injury (Bullock et al., 1998; Vespa et al., 1998; Marklund et al., 2006). A recent review addressed the failure of large, multicenter phase II clinical trial to produce an improvement in outcome in TBI

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patients (Marklund et al., 2006) and raised concern about the ability to translate from bench to bedside. (For detailed discussion of why therapies shown to be efficacious in animals failed to translate to human TBI, see recent reviews: (Statler et al., 2001; Cernak, 2005; Morales et al., 2005; Thompson et al., 2005; Marklund et al., 2006; Kokiko and Hamm, 2007).

In phase 3, secondary events—such as hypoxia, hypotension, ischemia, increased intracranial pressure (ICP) and brain swelling, and metabolic failure—perturb brain function further and augment cell injury (Statler et al., 2001; Graham et al., 2002; Marklund et al., 2006). As in phase 2, those secondary insults occur over an extended period of time postinjury and so are suitable targets for therapeutic intervention.

In human TBI, hypoxia and hypotension occur in one-third of patients with TBI (Morganti-Kossmann et al., 2007; Statler et al., 2001). Hypotension is a principal predictor of poor outcome after TBI: a single episode of systolic blood pressure of less than 90 mm Hg is associated with a 150% increase in mortality (Statler et al., 2001). In a recent prospective multicenter study, about 40% of patients with TBI sustained a secondary insult before reaching the hospital (Chi et al., 2006). Of those patients, 65% had episodes of hypoxia, 11% were hypotensive, and 24% showed a combination of those two secondary insults. Episodes of hypoxia were particularly notable in that they were independently predictive of death. Moreover, the episodes occurred despite aggressive medical management, including endotracheal intubation.

Posttraumatic ischemia has been demonstrated in both animal models and humans after TBI and is associated with poor neurologic outcome. The factors mediating posttraumatic ischemia include mechanical damage to blood vessels, hypotension in concert with autoregulatory failure, and lack of available endogenous vasomodulators, such as nitric oxide and prostaglandins (Werner and Engelhard, 2007).

Injury severity is a determinant of the magnitude of increase in ICP (Thompson et al., 2005). Increased ICP is usually a consequence of brain swelling that occurs in response to disruption of the blood–brain barrier and the later evolution of cerebral edema (Pasternak and Lanier, 2007). Edema has a profound effect on the brain because of the restrictions imposed by the bony calvarium, which limit further expansion of the edematous brain and lead to an increase in ICP.

Metabolic failure arises from mitochondrial dysfunction, reduced availability of the nicotinic coenzyme pool, and intramitochondrial overload (Werner and Engelhard, 2007). Outcome is worsened in accordance with the degree of metabolic failure (Werner and Engelhard, 2007). An alternative finding has been hypermetabolism of glucose, which reflects an uncoupling of cerebral blood flow and metabolism. It is a scenario whereby massive transmembrane ionic fluxes and neuroexcitation are not adequately met by increases in cerebral blood flow (Werner and Engelhard, 2007).

Phase 4, representing recovery and functional outcome, is influenced by primary and secondary injury responses and by wound-healing events, including phagocytic removal of cellular debris, glial scar formation, and plastic changes in neural networks. Recovery of function after brain injury is described in three phases (Wieloch and Nikolich, 2006). Phase 1 involves reversal of inhibition of function and initiation of cell repair, phase 2 entails a change in the properties of existing pathways, and phase 3 involves the formation of new connections (Wieloch and Nikolich, 2006). Efforts have been made to reverse secondary pathogenesis with

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an emphasis on extending treatment beyond the acute injury into this recovery phase (Kokiko and Hamm, 2007). One result is the concept that enhancing neuronal activity may facilitate cognitive recovery (Kokiko and Hamm, 2007). Strategies to support recovery also include early activation of noradrenergic, dopaminergic, and cholinergic pathways to promote functional plasticity and growth factors to support plasticity; cortical stimulation and physical therapy can enhance recovery during the chronic phase (Wieloch and Nikolich, 2006).

On the basis of the complex pathophysiology of TBI, there has been a concerted effort to develop biomarkers of injury that would serve as both diagnostic and prognostic measures of injury or recovery (Kochanek et al., 2008). The availability of cerebrospinal fluid, brain tissue, and interstitial fluid from both experimental models of TBI and brain-injured patients has made it possible to identify candidate biomarkers. Putative serum biomarkers of interest have included cyclic adenosine monophosphate, thought to be an indicator of depth of coma, and neuron-specific enolase, myelin basic protein, and S100B, markers of structural damage. In more recent years, proteomics and multibead technology, based on multiple enzyme immunosorbent assays (EIA), have been developed to assay multiple proteins from a relatively small sample. Those advanced technologies offer the opportunity to track the complex injury cascade that accompanies TBI and ultimately to generate a panel of biomarkers that can be applied to the brain-injured patient.

TRADITIONAL CLASSIFICATIONS OF TRAUMATIC BRAIN INJURY

TBI may be classified according to the extent of the pathology of the injury or according to the biomechanics of the injury. Both these classifications are discussed below.

CLASSIFICATION ACCORDING TO EXTENT OF PATHOLOGY

TBI has been described pathologically as focal and/or diffuse (Smith et al., 2003; Werner and Engelhard, 2007) (Figure 2.1). Focal damage is characterized by cerebral contusions resulting from forces related to impact (Povlishock and Katz, 2005). Contrecoup contusion may be apparent but is thought to be a consequence of acceleration and deceleration rather than impact (Graham et al., 2002). Diffuse injuries arise from rapid rotations of the head that result in tissue distortion or shear and typically occur in motor-vehicle collisions and less often in falls and assaults (Smith et al., 2003; Morales et al., 2005).

It is important to emphasize that focal and diffuse injuries overlap (Povlishock and Katz, 2005). Human TBI, particularly severe TBI, is heterogeneous (Graham et al., 2000; Faden, 2002). It is unusual to find a single lesion and more common to find both focal and diffuse patterns of damage. Moreover, the number of lesions increases in proportion to the severity of the injury and correlates with morbidity (Graham et al., 2000).

Pathologic Features of Focal Traumatic Brain Injury

Focal injuries are evidenced by lacerations, contusions, and hematomas resulting from overt vascular damage (Morales et al., 2005). Localization of a hematoma depends in part on which elements of the vascular tree are injured. Rupture of meningeal vessels, bridging veins, and intrinsic vasculature leads to extradural, subdural, and intracerebral hematomas, respectively.

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Intracerebral hematomas are commonly found in the gray matter or at boundaries between gray and white matter (Povlishock and Katz, 2005).

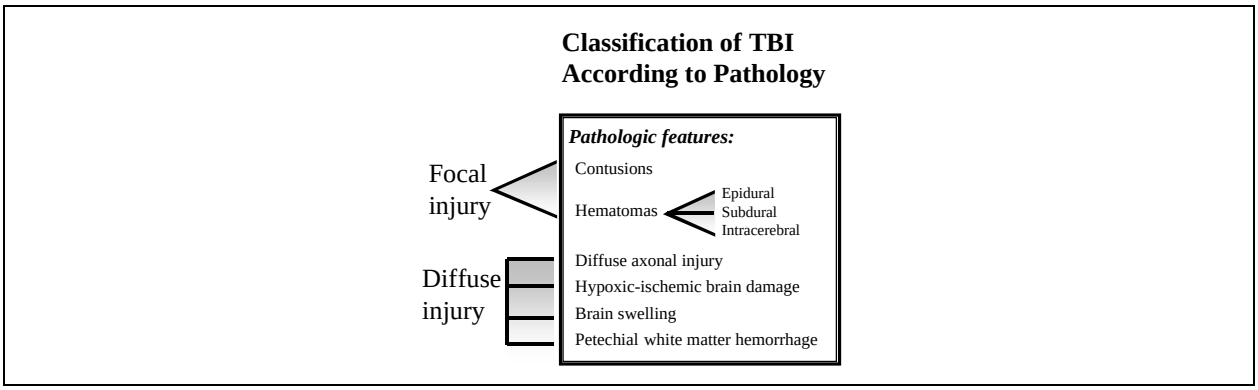

FIGURE 2.1 Pathologic classification of TBI.

Disruption of the blood–brain barrier is a feature of TBI, including focal insults. Trauma produces physical damage to blood vessels, manifested in part by hemorrhage. Barrier disruption allows entry of toxic molecules while also providing an avenue for delivery of therapeutic agents into the damaged tissues (Saunders et al., 2008). It is the latter that has prompted investigators to define the window of barrier disruption better. There is evidence that the barrier to plasma-protein–size molecules is about 4 hours, whereas smaller molecules (smaller than 10 kDa) can access the brain for up to 4 days (Saunders et al., 2008). In the head-injured patient, disruption of the barrier is associated with life-threatening cerebral edema and is the basis of treatment with intravenous hyperosmolar solutions. However, the mechanism of action is not clearly understood, and there is no gold standard, on the basis of evidence from a clinical trial, of its effectiveness (Narayan et al., 2002).

Neuronal injury is also a feature of focal TBI. However, the patterns of neuronal injury are not necessarily restricted to contusional and pericontusional cortical sites (Raghupathi, 2004). Neuronal loss has been reported in more remote regions, including the hippocampus (Cortez et al., 1989; Kotapka et al., 1992; Lowenstein et al., 1992; Hicks et al., 1996), thalamus (Hicks et al., 1996; Sato et al., 2001), and the cerebellum (Sato et al., 2001; Park et al., 2006; Ai et al., 2007; Igarashi et al., 2007) in experimental models of TBI. Similar findings are seen in human TBI (Adams et al., 1985; Kotapka et al., 1992; Raghupathi, 2004).

At the contusional site, neuronal injury is apparent within hours after trauma. Neurons initially appear swollen and with time assume a shrunken phenotype bearing a pyknotic nucleus, swollen mitochondria, and vacuolated cytoplasm. The volume of the lesion expands coincidentally with a chronic pattern of neuronal degeneration (Colicos et al., 1996; Hicks et al., 1996; Bramlett et al., 1997; Conti et al., 1998; Raghupathi, 2004).

Pathologic Features of Diffuse Traumatic Brain Injury

Four pathologic conditions have been attributed to diffuse TBI: traumatic axonal injury, hypoxic brain damage, brain swelling, and vascular injury (Morales et al., 2005; Povlishock and Katz, 2005). The disabling symptoms seen in TBI can arise from widespread traumatic axonal damage (Hurley et al., 2004; Morales et al., 2005) that is evident in postmortem brains after mild, moderate, or severe injury (Morales et al., 2005).

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Diffuse axonal injury, an important predictor of outcome (Graham et al., 2002), evolves over hours to days and is characterized by axonal swellings and bulbs (Hurley et al., 2004). Primary axotomy, that is, the severing of an axon, is rare in human TBI and is associated with severe TBI. Diffuse axonal injury may culminate in axotomy, but this process is likely delayed in onset, beginning 12–24 hours after injury (Moppett, 2007). It was originally thought that mechanically induced damage to axons impaired axonal transport and that this impairment led to axonal swelling and ultimately axonal disconnection. Recent work, however, has shed light on the pathobiology of axonal injury (Povlishock and Katz, 2005). Although tearing of the axon may occur, it is usually limited to more severe injuries. Rather, axonal injury evolves as a consequence of focal changes in the plasmalemma, including altered permeability, which ultimately impede axonal transport. Data suggest that altered axolemmal permeability allows the influx in calcium and the subsequent activation of proteases that then disrupt the cytoskeleton. Under conditions of normal transport kinetics, focal swelling occurs as a consequence of the buildup of transported molecules and leads ultimately to disconnection of the axon.

Traumatic axonal swellings are not the only indicator of axonal damage. In fact, cytoskeletal perturbations after TBI need not culminate in axonal swellings (Povlishock and Katz, 2005). Rather, there may be a switch from anterograde to retrograde transport, which prevents the buildup of transported molecules (Povlishock and Katz, 2005). The complexity of axonal injury is also evidenced by recent studies of unmyelinated fiber tracts that showed that ionic dysregulation contributes to impairment of anterograde transport (Iwata et al., 2004). There are also data that show that unmyelinated, small-caliber axons may be particularly vulnerable to TBI (Reeves et al., 2005) and may play an important role in morbidity.

Hypoxia, brain swelling, and vascular injury are also seen in diffuse injuries (see above as a description of those events is provided in more detail).

CLASSIFICATION ACCORDING TO BIOMECHANICS OF INJURY

Human head injury is also categorized according to the type of primary injury, either closed (blunt and not caused by a missile) or penetrating injuries (Graham et al., 2002; Morales et al., 2005) (Figure 2.2).

Closed Injury

Closed injury includes static and dynamic loading. Static loading occurs when a gradual force is applied to the brain whereas dynamic loading is characterized by rapid acceleration and deceleration. Static loading is not common in human head injury. It may occur in victims of natural disasters, such as earthquakes and landslides, who become trapped under heavy debris. In such a scenario, the head is particularly vulnerable to injury imposed by a gradual force, greater than 200 ms (Graham et al., 2002).

Dynamic loading is more common in human brain injury and is associated with rapid acceleration and deceleration of the brain (Graham et al., 2002). In contrast with static loading, the forces associated with dynamic loading occur in less than 200 ms. Outcome is governed by tissue strain, which is defined as the amount of deformation that occurs as a consequence of the force applied to the brain (Graham et al., 2002; Morales et al., 2005).

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Tolerance of deformation varies with the type of tissue: bone is the strongest, and neural and vascular elements are the most vulnerable (Graham et al., 2002). Tensile strain and shear strain are the two types that most commonly cause damage to the vasculature and brain (Graham et al., 2002).

Dynamic loading is categorized as either impulsive or impact loading. Impulsive loading occurs when the head is stopped or set into motion by an indirect impact, such as a blow to the thorax. Head injury results from the inertia produced by the movement of the head. Impact loading, the more common form of dynamic loading, results when a blunt object strikes the head. Inertia and contact occur in combination. An example would be deceleration of the head when a moving automobile strikes a tree and then the driver's head strikes the steering wheel.

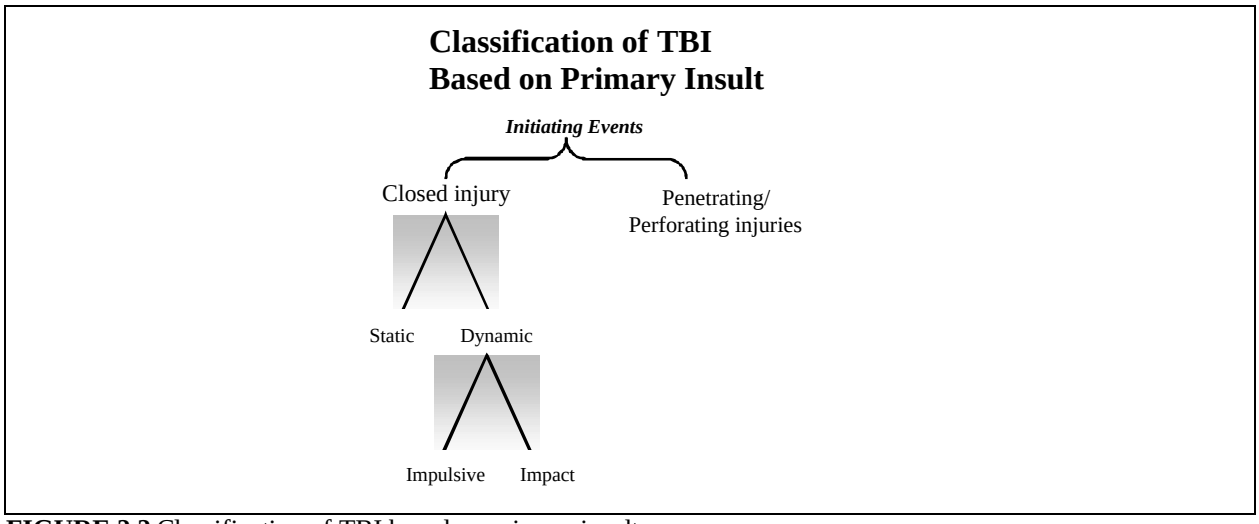

FIGURE 2.2 Classification of TBI based on primary insult.

Penetrating and Perforating Injuries

Missile injuries, such as gunshot wounds, are a common cause of TBI. These injuries are classified as either penetrating or perforating depending on how the missile traverses the head (Graham et al., 2002). In penetrating injuries, the object enters and lodges within the cranial cavity. Perforating injuries occur when the object traverses the cranial cavity and leaves through an exit wound. The extent of damage is governed by features of the missile (shape and mass) and by its direction and velocity (Morales et al., 2005). Damage is also related to the amount of energy that is released in passage through the brain (Graham et al., 2002). Although brain damage is often severe, there are instances when the bullet bypasses critical centers and the person maintains consciousness (Graham et al., 2002).

THERAPEUTICS AND TRAUMATIC BRAIN INJURY

A number of recent reviews have addressed pharmacologic strategies of treatment for TBI (Faden, 2002; Morales et al., 2005; Thompson et al., 2005; Marklund et al., 2006; Schouten, 2007). The strategies have targeted secondary injury cascades, including those related to excitotoxicity, calcium channels, oxidative stress, inflammation, cell-death pathways, calpains, endocrine-related abnormalities, altered neurotransmission, and growth factors (Marklund et al., 2006). Pharmacologic blockade targeting those pathways has improved the outcome in animal

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models of TBI, but clinical trials have failed to reproduce the benefit seen in those studies (Faden, 2002; Marklund et al., 2006). The failure to translate to success in human TBI may reflect both limitations of the experimental model and differences in the design of the animal studies (Faden, 2002; Faden and Stoica, 2007) and has led to consideration of developing a model that would be more relevant to human TBI (Morales et al., 2005). It has been suggested that no single animal model can accurately reproduce the complex, heterogeneous human TBI (Morales et al., 2005). It is also possible that the current models should be refined to involve a more comprehensive experimental design that includes dose-response studies in concert with measures of both behavior and pathology; incorporates secondary insults, such as hypotension, hypovolemia, and hypoxia, that are seen in human TBI; addresses the consequences of repeated brain injuries; considers age and sex as variables in the experimental design; and provides monitoring of measures (cerebral perfusion pressure, ICP, blood pressure, and blood gases) that would parallel those used in the management of human TBI (Statler et al., 2001; Faden, 2002; Morales et al., 2005; Thompson et al., 2005). Finally, with the recommendation to develop a classification for human TBI based on pathoanatomic measures (Saatman et al., 2008), future efforts to develop and/or refine animal models will need to consider the findings that emerge from this clinical effort.

SUMMARY OF PATHOBIOLOGY OF TRAUMATIC BRAIN INJURY

The pathobiology of TBI can be summarized as follows:

- The traditional classifications of TBI have been based on the type of injury (focal vs diffuse) and on the biomechanics of the primary injury (closed and missile injuries). The primary insults damage both gray and white matter and initiate secondary pathogenic events at the cellular, biochemical, and molecular levels that collectively mediate widespread damage.
- The final common pathways for TBI are similar despite differences in the initiating event. For example, calcium-mediated activation of neurotoxic factors, production of free radicals, and mitochondrial dysfunction are general features of TBI. However, regional patterns of vulnerability and the magnitude and kinetics of those downstream events are governed by the initiating event.
- Unlike animal models that are designed to reproduce a particular characteristic of TBI, human TBI is characteristically heterogeneous, particularly after a severe injury, with features of both focal and diffuse brain damage. The diversity of clinical outcomes reflects that heterogeneity at least in part.

Although this chapter is focusing on TBIs that are typically seen in civilians, an emerging field of research addresses brain injuries related to the military. This research includes missile-related and blast-induced brain injuries. What is clear from the effort to date is that the pathobiology of military TBIs, particularly blast injuries, has characteristics not seen in other types of brain injury, despite similar secondary injury cascades.

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TRAUMATIC BRAIN INJURIES RELEVANT TO THE MILITARY

Throughout Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF), explosive devices have become more powerful, their detonation systems more creative, and their additives more devastating. According to the Department of Defense (DoD) "Personnel and Procurement Statistics", 75% of all US military casualties in OEF and OIF are caused by explosive weaponry (DMDC, 2008). As of January 2008, DoD reported that over 5,500 soldiers had suffered TBIs (CRS, 2008). As a continuing threat to troops, blast injury, especially BINT, has been called the signature wound of the war in Iraq. Explosive devices are also used against civilians. Indeed, the use of explosive weaponry is the most common cause of casualties in terrorist incidents. Terrorists increasingly use suicidal-homicidal bombers that deliberately accompany the explosive device, often wearing it, to ensure the maximal harm. The bombers walk or drive into buses, subways, residential areas, shopping malls, and government buildings.

FIGURE 2.3 Potential consequences of blast exposure.

In both civilian and military environments, exposure to a blast (see Figure 2.3) might cause instant death, injuries with immediate manifestation of symptoms, or injuries with delayed manifestation.

Protection from blast injuries presents several challenges. Body armor protects from shrapnel and projectiles, but it also constitutes an improved contact surface for shock-front–body interaction and energy transfer and may also serve as a reflecting surface that can concentrate the power of an explosion as the blast wave is reflected by the armor front and back (Phillips et al., 1988). The improved interceptive properties of body armor have increased the survival rate of soldiers by protecting them from penetrating injuries. In parallel with the increased survival rate, however, the rate of severe debilitating long-term consequences has also increased (Warden, 2006). Moreover, besides being acutely injured, soldiers serving in theater and some military professionals during their daily activity or training are also subjected to repeated low-level blast

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exposure. The cumulative effects of the exposures might lead to serious short-term and long-term health impairments (Richmond et al., 1981). For those without body armor, the effects of blast are more deadly, and the whole spectrum of blast injuries can be seen (Table 2.3). Apart from the injuries caused by blast overpressure (primary blast effects), they have an increased potential for penetrating injuries from shrapnel and other debris (secondary blast effects) and for acceleration and deceleration of the body and head (tertiary blast effects) (Figure 2.6). Moreover, although barriers and check points may be used to prevent vehicles and personnel carrying explosives from entering a facility, in urban areas it may not be possible to achieve the recommended standoff distances shown in Table 2.1, and even those distances may not be adequate to prevent BINT injuries.

BASIC MECHANISMS OF EXPLOSIVE INJURIES

Physics

A blast wave generated by an explosion starts with a single pulse of increased air pressure that lasts a few milliseconds. The negative pressure or suction of the blast wave follows the positive wave immediately (Owen-Smith, 1981). The duration of the blast wave—that is, the time that an object in the path of the shock wave is subjected to the pressure effects—depends on the type of explosive and the distance from the point of detonation (Clemedson, 1956). Table 2.1 summarizes the safety zones—that is, the standoff distances—for various types of bomb explosions.

TABLE 2.1 Safety Recommendations for Standoff Distances from Different Types of Exploding Bombs

Container or Vehicle Description	Maximum Explosives Capacity	Lethal Air-Blast Range	Maximum Evacuation Distance	Falling-Glass Hazard
Pipe 2 x 12 in	5-6 lb		850 ft (259 m)	
Pipe 4 x 12 in	20 lb			
Pipe 8 x 24 in	120 lb			
Bottle 2 L	10 lb			
Bottle 2 gal	30 lb			
Bottle 5 gal	70 lb			
Boxes or shoebox	30 lb			
Briefcase or satchel bomb	50 lb		1,850 ft (564 m)	1,250 ft (381 m)
1-ft^3 box	100 lb			
Suitcase	225 lb		1,850 ft (564 m)	1,250 ft (381 m)
Compact sedan	500 lb in trunk	100 ft (30 m)	1,500 ft (457 m)	1,250 ft (381 m)
Full-size sedan	1,000 lb in trunk	125 ft (38 m)	1,750 ft (534 m)	1,750 ft (534 m)
Passenger van or cargo van	4,000 lb	200 ft (61 m)	2,750 ft (838 m)	2,750 ft (838 m)
Small box van	10,000 lb	300 ft (91 m)	3,750 ft (1,143 m)	3,750 ft (1,143 m)
Box van or water or fuel truck	30,000 lb	450 ft (137 m)	6,500 ft (1,982 m)	6,500 ft (1,982 m)
Semitrailer	60,000 lb	600 ft (183 m)	7,000 ft (2,134 m)	7,000 ft (2,134 m)

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NOTE: Table compiled from several publications of the Advanced Technical Group (ATG) for Blast Mitigation and Technical Support Working Group (TSWG).
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The blast wave progresses from the source of the explosion as a sphere of compressed and rapidly expanding gases, which displaces an equal volume of air at a high velocity (Rossle, 1950). The velocity of the blast wave in air may be extremely high, depending on the type and amount of the explosive used. The blast wave is the main determinant of the primary blast injury and consists of the front of high pressure that compresses the surrounding air and falls rapidly to negative pressure. It travels faster than sound and in few milliseconds damages the surrounding structures. The blast wind following the wave is generated by the mass displacement of air by expanding gases; it may accelerate to hurricane proportions and is responsible for disintegration, evisceration, and traumatic amputation of body parts. Thus, a person exposed to an explosion will be subjected not only to a blast wave but to the high-velocity wind traveling directly behind the shock front of the blast wave (Rossle, 1950). A hurricane-force wind traveling about 200 km/h exerts overpressure of only 1.72 kPa (0.25 psi), but a blast-induced overpressure of 690 kPa (100 psi) that causes substantial lung damage and might be lethal travels at about 2,414 km/h (Owen-Smith, 1981).

The magnitude of damage due the blast wave depends on the peak of the initial positive-pressure wave (an overpressure of 414–552 kPa or 60–80 psi), is considered potentially lethal, the duration of the overpressure, the medium of the explosion, the distance from the incident blast wave, and the degree of focusing due to a confined area or walls. For example, explosions near or within hard solid surfaces become amplified two to nine times because of shock-wave reflection (Rice and Heck, 2000). Moreover, victims positioned between the blast and a building often suffers 2–3 times the degree of injury of a person in an open space. Indeed, people exposed to explosion rarely experience the idealized pressure-wave form, known as the Friedländer wave. Even in open-field conditions, the blast wave reflects from the ground, generating reflective waves that interact with the primary wave and thus changing its characteristics. In a closed environment (such as a building, an urban setting, or a vehicle), the blast wave interacts with surrounding structures and creates multiple wave reflections, which, interacting with the primary wave and between each other, generate a complex wave (Mainiero and Sapko, 1996; Ben-Dor et al., 2001) (Figure 2.4). Table 2.2 summarizes the effects of different levels of overpressure on material surrounding the explosion and unprotected persons exposed to blast.

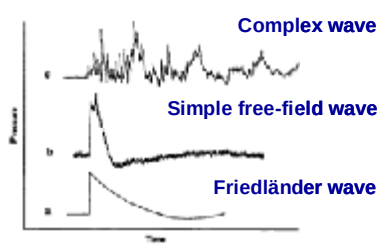

FIGURE 2.4 Explosion-induced shock waves: a) idealized representation of pressure-time history of an explosion in air; b) shock wave in open air; c) complex shock-wave features in closed or urban environment.
SOURCE: Mayorga, 1997. Reprinted with permission from Elsevier Science, Ltd. 2008.

Previous attempts to define the mechanisms of blast injury suggested the involvement of spalling, implosion, and inertial effects as major physical components of the blast-body interaction and later tissue damage (Benzinger, 1950). Spallation is the disruption that occurs at

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the boundary between two media of different densities; it occurs when a compression wave in the denser medium is reflected at the interface. Implosion occurs when the shock wave compresses a gas bubble in a liquid medium, raising the pressure in the bubble much higher than the shock pressure; as the pressure wave passes, the bubbles can re-expand explosively and damage surrounding tissue (Benzinger, 1950; Chiffelle, 1966; Phillips, 1986). Inertial effects occur at the interface of the different densities: the lighter object will be accelerated more than the heavier one, so there will be a large stress at the boundary. Recent results suggest that there is a frequency dependence of the blast effects: high frequency (0.5–1.5 kHz) low-amplitude stress waves target mostly organs that contain abrupt density changes from one medium to another (for example, the air-blood interface in the lungs or the blood–parenchyma interface in the brain), and low-frequency (<0.5 kHz) high-amplitude shear waves disrupt tissue by generating local motions that overcome natural tissue elasticity (for example, at the contact of gray and white brain matter).

Explosions may cause four major patterns of injury: primary blast injury caused by the blast wave itself, secondary injury caused by the fragments of debris propelled by the explosion, tertiary injury due to the acceleration of the body or part of the body by the blast wind, and flash burns due to the transient but intense heat of the explosion (Mellor, 1988).

TABLE 2.2 Overpressure Effects on Surrounding Materials and Unprotected Persons

Pressure, kPa (psi)	Effects on Material	Pressure, kPa (psi)	Effects on Unprotected Person
0.69–34.47 (0.1–5)	Shatter single-strength glass	34.47 (5)	Slight chance of eardrum rupture
6.89–13.79 (1–2)	Crack plaster walls, shatter asbestos sheet, buckle steel sheet, failure of wood wall	103.42 (15)	50% chance of eardrum rupture
13.79–20.68 (2–3)	Crack cinder-block wall, crack concrete block wall	206.84–275.79 (30–40)	Slight chance of lung damage
13.79–55.16 (2–8)	Crack brick wall	551.58 (80)	50% chance of severe lung damage
34.47–68.95 (5–10)	Shatter car safety glass	689.48 (100)	Slight chance of death
		896.32–1,241.06 (130–180)	50% chance of death
		1,378.95–1,723.69 (200–250)	Death usual

SOURCE: Owen-Smith, 1981.

General Medical Effects

In general, primary blast injuries are characterized by the absence of external injuries and by potential parenchymal damage, mostly of the lungs (Rossle, 1950; Chiffelle, 1966); thus, internal injuries are often unrecognized, and their severity underestimated (Dedushkin et al., 1992). Table 2.3 summarizes some of the injuries induced by concomitant primary, secondary, tertiary, and quaternary blast effects as defined by the Centers for Disease Control and Prevention (CDC, 2003).

According to the latest experimental results, the extent and types of primary blast-induced injuries depend not only on the peak of the overpressure but on other characteristics,

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such as the number of overpressure peaks, the lag between overpressure peaks, the shear fronts between overpressure peaks, frequency resonance, and electromagnetic pulse.

Previously, exposure to blast overpressure was considered to damage primarily gas-containing organs or those containing structures of different specific weights (such as ears, lungs, and the gastrointestinal tract) (Benzinger, 1950; Clemedson, 1956; Phillips and Zajtchuk, 1989). Therefore, most research focused on the mechanisms of blast injuries within gas-containing organs or organ systems, primary blast-induced neurotrauma was underestimated, and safety recommendations (Table 2.1) focused on the injurious effects of blast on extracerebral body parts and organs and not on hidden brain damage and potential neurologic consequences.

TABLE 2.3 Summary of Most Important Body-System Injuries Induced by Concomitant Primary, Secondary, Tertiary, and Quaternary Effects of Blast

System	Injury or Pathologic Condition
Auditory system	Eardrum rupture
	Disruption of ossicles
	Cochlear damage
Respiratory system	Blast lung[a]
	Hemothorax
	Pneumothorax
	Pulmonary contusion
	Pulmonary hemorrhage
	Airway epithelial damage
	Aspiration pneumonitis
	Sepsis
	Arteriovenous fistula (air embolism)
Gastrointestinal system	Bowel perforation
	Hemorrhage, fracture, rupture of liver or spleen
	Mesenteric ischemia caused by air embolism
	Sepsis
Nervous system[b]	Concussion
	Closed (blunt) brain injury
	Open (penetrating) brain injury
	Stroke from air embolism
	Spinal-cord injury
Cardiovascular system	Myocardial contusion
	Myocardial infarction from air embolism
	Cardiogenic shock
	Peripheral vascular injury
	Peripheral ischemia from air embolism
	Shock
Genitourinary system	Renal contusion
	Renal laceration
	Acute renal failure due to shock or rhabdomyolysis
	Testicular rupture
Visual system[c]	Perforated eye globe
	Foreign bodies in eye
	Air embolism
	Orbital fractures

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System	Injury or Pathologic Condition
Extremities	Fractures
	Amputations
	Crush injuries
	Compartment syndrome
	Burns
	Cuts
	Lacerations
	Acute occlusion of artery
	Air-embolism–induced injury

[a]Blast lung is a direct and best known consequence of a high-energy overpressure wave; it is the most common fatal primary blast injury in initial survivors of an explosion.
[b]Primary blast effects can induce blast-induced neurotrauma without a direct blow to the head.
[c]Up to 10% of unprotected blast survivors have substantial eye injuries.
NOTE: Information added to the original table as compiled by Centers for Disease Control and Prevention.
SOURCE: CDC, 2003.

Complex morphologic and functional impairments caused by blast injuries are often underestimated. Survivors of blast injury commonly experience apathy, lethargy, and psychomotor dystonia and rarely convulsion and paralysis (Ascroft and Lond, 1940; Stewart and Russel, 1941; Garai, 1944; Huller and Bazini, 1970; Harmon and Haluszka, 1983). Deafness, tinnitus (Phillips and Zajtchuk, 1989; Khil'ko et al., 1997; Cripps et al., 1999), thoracic pain, and vertigo are the most common subjective sensations in people who were near an explosion (Cernak et al., 1999b). The specific clinical signs that might be seen in a physical examination on admission are scanty and irregular: cyanosis; blood oozing from the nose, mouth, and ears; tympanic membrane hyperemia, hemorrhage, or rupture (Phillips and Zajtchuk, 1989); tachypnea preceded by a short period of apnea, dyspnea, hemoptysis, or moist crepitations in both lung fields (Damon et al., 1968; Mellor, 1988; Hirshberg et al., 1999; Lavery and Lowry, 2004); tachycardia; and decrease in mean arterial pressure (Guy et al., 1998; Weiss et al., 1999). Chest radiography may reveal pneumothorax, bilateral intrapulmonary hemorrhage, and edema with a characteristic pattern called snowstorm (Caseby and Porter, 1976). Electrocardiographic examination rarely shows specific signs; it might occasionally show alterations similar to those of myocardial ischemia or infarction (Cooper et al., 1983). Measurement of some readily available biochemical characteristics in the blood (serum enzymes, blood-urea nitrogen, leukocyte count, and hemoglobin concentration) fails to aid in the diagnosis of blast injury (Harmon et al., 1988). Some clinical (Cernak et al., 1999a) and experimental studies (Cernak et al., 1996a; Huang et al., 1996) have shown that measurement of sulfidopeptide leukotrienes (sLTs: LTC4, D4, and E4) and of 6-keto-PGF1α and TxB2, the stable products of prostacyclin (PGI2) and thromboxane A2 (TxA2), respectively, and identification of those compounds in the plasma would be a useful tool for diagnosing blast injuries in the early stage. Indeed, it has been reported that patients with blast injury had significantly higher mean circulating TxB2 and sLT concentrations and significantly lower plasma 6-keto-PGF1α:TxB2 ratio during the 5 days after injury than patients with the most severe injuries but without blast injury (Cernak et al., 1999a). Because of the complexity of blast injury, its diagnosis should be based on a history of blast exposure, the presence of subjective symptoms characteristic of blast injuries, pathognomonic findings in a physical examination, and suggestive results of clinical tests (Cernak et al., 1999a; 1999b) (Figure 2.5).

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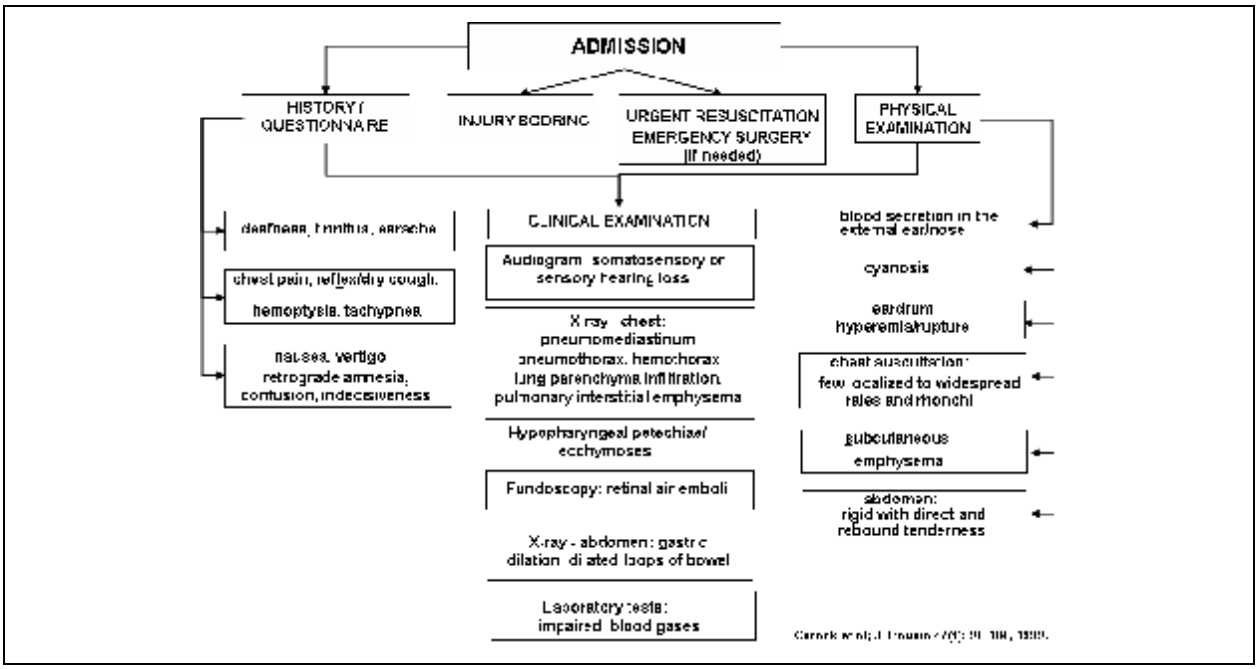

FIGURE 2.5 Examination and diagnosis algorithm for blast injuries.
SOURCE: Cernak et al., 1999a. Reprinted with permission from Lippincott Williams and Wilkins, 2008

Blast-Induced Neurotrauma

There is an outdated dogma that neurologic impairments caused by primary blasts are rare because the skull provides excellent protection for the brain; that is, brain injury is solely a consequence of air emboli in cerebral blood vessels (Clemedson, 1956; Owen-Smith, 1981). Despite recent clinical findings (Cernak et al., 1999a; 1999b; 1999c; 2000), experimental findings (Saljo et al., 2000; Cernak et al., 2001a; 2001b), and experience in contemporary military operations that suggest substantial short-term and long-term neurologic deficits caused by blast exposure without a direct blow to the head, old belief prevails in the professional literature and in clinical practice. Indeed, information on blast injuries (Table 2.3) lists mainly the consequences of secondary and tertiary blast mechanisms. Although BINT is one cause of in-theater injuries, it is often underdiagnosed. Its complex clinical syndrome is caused by the combination of all blast effects (Figure 2.6).

It is noteworthy that blast injuries are usually manifested in a form of polytrauma, that is, injury involving multiple organs or organ systems. Primary blast injury of the chest produces bradycardia, hypotension, and apnea via vagal reflexes, which may induce cerebral hypoxia and ischemia (Cernak et al., 1996a; 1997; Ohnishi et al., 2001). Bleeding from injured organs, such as the lungs and intestine, causes a lack of oxygen in all vital organs, including the brain. Damage of the lungs reduces the surface for oxygen uptake from the air and reduces the amount of the oxygen delivered to the brain (Cernak et al., 1997). Tissue destruction initiates the synthesis and release of hormones and mediators into the blood that, when delivered to the brain, change the brain's function (Cernak et al., 1996b). Irritation of the nerve endings in injured peripheral tissue and organs also contributes to BINT (Irwin et al., 1999).

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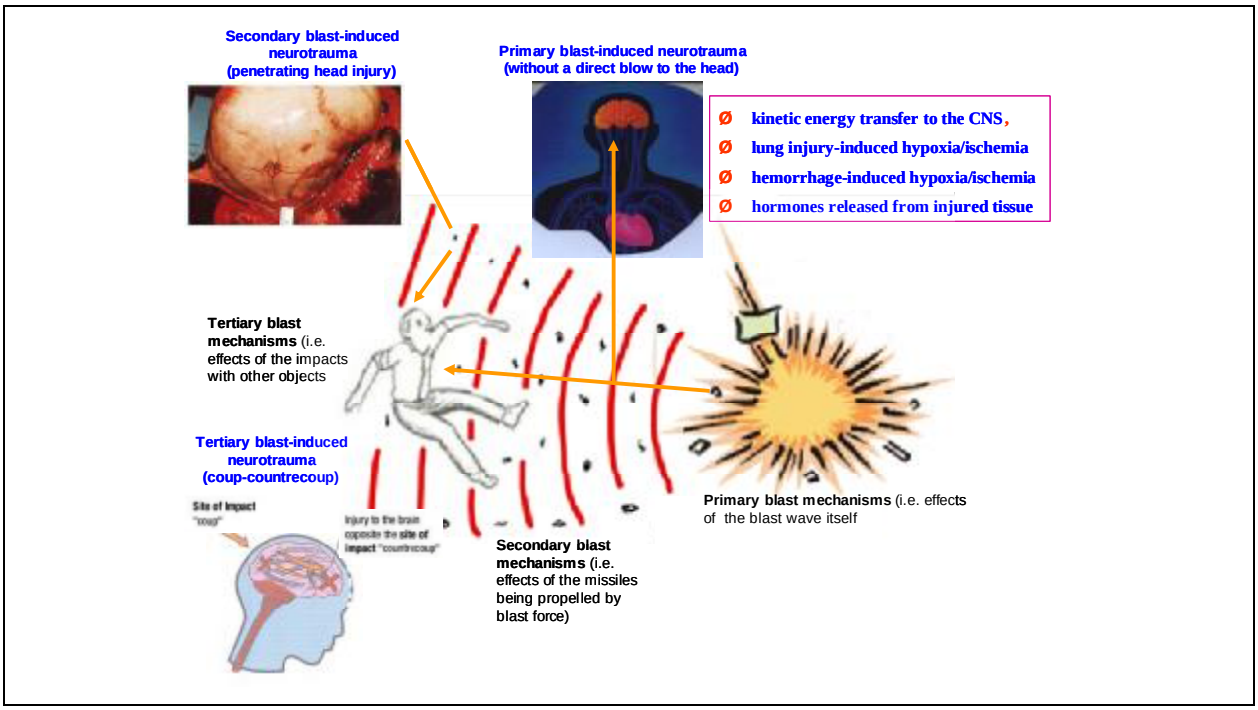

FIGURE 2.6 Complex mechanisms of blast-induced neurotrauma.
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Primary-Blast–Induced Neurotrauma

There are theories of the vital mechanisms of blast-wave–brain interaction underlying primary BINT. There are numerous assumptions that explain BINT as a type of postconcussion syndrome, that emphasize the psychologic dimension of blast experience (Jones et al., 2007), or, on the basis of clinical and experimental data, that posit that BINT can develop without a direct blow to the head and results from the kinetic-energy transfer of the blast wave through large blood vessels in the abdomen and chest to the central nervous system (Cernak et al., 1999a; 2001b; Bhattacharjee, 2008). As the front of the blast overpressure interacts with the body surface and compresses the abdomen and chest, it transfers its kinetic energy to the body's fluid phase. The resulting hydraulic interaction initiates oscillating waves that traverse the body at about the speed of sound in water and deliver the kinetic energy of the blast wave to the brain. Once delivered, that kinetic energy causes both morphologic and functional damage in distinct brain structures. Although the damage might resemble the injury patterns that develop after mechanical TBI caused by direct interaction of a mechanical force and the skull, the injury manifestation, timeline, and complexity of pathologic changes make BINT a distinct health problem. Furthermore, frequency resonance between blast wave and electromagnetic pulse might also contribute to primary-blast–induced neurologic disturbances (G. Ling, personal communication).

Experimental Studies. Experimental studies on primary-blast–induced biologic effects routinely use shock tubes or blast tubes, cylindrical metal tubes usually closed at one end. The blast overpressure and underpressure waves are generated either by compressed air (shock tubes) or by detonation of an explosive (blast tubes) in the closed end of the tube (Nishida, 2001; Robey, 2001). Anesthetized animals are fixed individually in special holders designed to prevent

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any movement of their bodies in response to blast and thus to prevent tertiary effects of the shock or blast wave (Wang et al., 1998; Cernak, 2005). Most shock and blast tubes used in current experimental models replicate the ideal blast wave from an open-air explosion without a capability to generate a nonideal blast wave with multiple shock and expansion fronts as seen in real-life conditions, and this limits the extent of comparability of experimental and clinical findings. A small number of studies use open-field exposure of animals to a blast wave generated by detonation of an explosive (Richmond, 1991; Cernak et al., 1996b; 1997; Axelsson et al., 2000; Saljo and Hamberger, 2004). Although such an experimental setting is more comparable with in-theater conditions, the physical characteristics (such as homogeneity of the blast wave) are less controllable, so a broader range of biologic response should be expected. A wide range of blast overpressure sustained for various durations has been used in single-exposure experimental studies. In most studies, the animals were subjected to a shock or blast wave with a mean peak overpressure of 52–340 kPa (7.54–49.31 psi) on the nearest surface of an animal's body (Clemedson et al., 1969; Saljo et al., 2000; Cernak et al., 2001b; Chavko et al., 2007). Most experiments used rodents (mice and rats), but some have subjected nonhuman primates or other larger mammals to blast (Richmond et al., 1967, 1968; Bogo et al., 1971; Bowen et al., 1968; Damon et al., 1968).

Considerable reductions in food intake and exercise performance have been found in rats exposed to low-intensity shock waves (83 kPa or 129 kPa) (Bauman et al., 1997). Similar findings have been reported in sheep (Mundie et al., 2000). Exposure to blast has been described as inducing hyperactivation of the autonomous nervous system and, via activation of such vagovagal reflexes as the Bezold–Jarisch reflex, causing bradycardia (Cernak et al., 1996b). Indeed, bilateral vagotomy before blast exposure prevented depression of cardiovascular functions and prevented pulmonary edema in rabbits subjected to a shock wave of about 300 kPa (43 psi). Rhesus monkeys exposed to about 207 kPa (30 psi), about 276 kPa (40 psi), or about 345 kPa (50 psi) had significant albeit transient memory and performance deficits (Bogo et al., 1971). Considerable and persistent memory deficits have been shown in rats subjected to blast waves generated in an air-driven shock tube (Cernak et al., 2001a). Rats exposed to different charges of a plastic explosive (pentaerythritol tetranitrate), intended to generate a blast wave of 220 or 350 kPa in a blast tube, demonstrated significant decreases in amplitude and frequency of the brain's electric activity measured with electroencephalography (EEG) continuously during 30 minutes after the blast (Risling et al., 2002). Those changes were more profound in rats exposed to 350 kPa or in those exposed repeatedly to 220 kPa. Similarly, transient flattening of the EEG was seen in pigs immediately after the blast, in contrast with the unchanged baseline EEG in control animals. That momentary depression of cortical activity was accompanied by brief apnea indicates a blast-wave–induced effect on the brainstem or higher controlling center (Axelsson et al., 2000).

Blast exposure has been reported to cause brain edema and considerable metabolic disturbances in the brain: significantly decreased glucose, magnesium, and ATP concentrations; increased lactate concentration and lactate:pyruvate ratio (Cernak et al., 1996b); and impaired function of the sodium-potassium ATPase pump (Cernak et al., 1997). Those changes clearly suggest energy failure or imbalance between energy demand and available energy, shift of glucose metabolism from the aerobic toward the anaerobic pathway, and impairment in neuronal cell membrane permeability (Cernak et al., 1997). Swelling of neurons, an astroglial response, and myelin debris in the hippocampus have been found after moderate blast injury in animals (Cernak et al., 2001b). Immunohistochemical analyses have shown significant damage to the

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neuronal cytoskeleton in layers II–IV of the temporal cortex, in the cingulated gyrus and the pirifom cortex, in the dentate gyrus, and in the CA1 region of the hippocampus over 7 days after blast exposure (Saljo et al., 2000). Oxidative stress, changes in antioxidant–enzyme defense systems (Cernak et al., 2001a; 2001b), increase in nitric oxide metabolism, and later cognitive deficits (Cernak et al., 2001a) have also been seen.

Studies on the effects of repeated low-level (29–62 kPa) blast exposures demonstrated accumulating pathologic alterations involving multiple organs or organ systems (Yang et al., 1996; Elsayed and Gorbunov, 2007), with activation of the hypothalamic–pituitary–adrenal axis and significant biochemical and hormonal changes in the brain (Mazurkiewicz-Kwilecki, 1980). Moreover, repeated exposures to low-intensity (20 kPa) blast caused significant motor deficits in rats (Moochhala et al., 2004).

Clinical Studies. Experimental data and clinical observations suggest the involvement of multiple mechanisms in the development of brain damage and associated functional impairments and disabilities in those exposed to blasts. People exposed to blast frequently manifest loss of memory of events before and after the explosion, confusion, headache, impaired sense of reality, and reduction in decision-making ability (Cernak et al., 1999a; 1999b; Taber et al., 2006; Warden, 2006). Patients with brain injuries acquired in explosions often develop sudden, unexpected brain edema and cerebral vasospasm despite continuous monitoring (Armonda et al., 2006). Significant changes in blood chemistry suggest development of oxidative stress, electrolyte imbalance, and neuroendocrine alterations in blast casualties during the acute posttraumatic phase (Cernak et al., 1999a; 1999b; 1999c; 2000). The onset of mild BINT symptoms might be latent, occurring months or even years after the event. The symptoms include weight loss, hormonal imbalance, chronic fatigue and headache, and problems in memory, speech, and balance (Taber et al., 2006; Scherer, 2007). A study of patients subjected to explosion but with no visible injuries or only lower-extremity wounds has demonstrated that 51% had neurologic symptoms (such as headache, insomnia, psychomotor agitation, and vertigo); of those 36% had EEG alterations during the acute stage, such as hypersynchronous, discontinuous, or irregular brain activity. Both neurologic and EEG alterations progressed to the chronic stage in 30% of that group (Cernak et al., 1999a; Taber et al., 2006). Trudeau et al. reported that even veterans with a remote history of blast injury display permanent EEG changes similar to those often found after TBI, as well as persistent cognitive problems (Trudeau et al., 1998). In the study of male combat veterans, Yehuda (1999) suggested linking the memory dysfunction and the neuroendocrine alterations of posttraumatic stress with the neuroanatomic findings of reduced hippocampal volume. That opinion is consistent with the previously mentioned results published by Trudeau et al. (1998). Moreover, clinical studies involving blast-injured patients from the Afghanistan war reported biochemical alterations in the cerebrospinal fluid (CSF) suggestive of increased activity of cytoplasmic mitochondrial proteolytic enzymes; those changes have been shown to be directly related to the severity of brain trauma (Khil'ko et al., 1995a). Moreover, primary BINT has been shown to induce specific immune responses with increased concentrations of immunoglobulin G and immunoglobulin A in the CSF and increased circulation of immune complexes and altered function of the immune system that sometimes led to permanent immune deficiency (Khil’ko et al., 1995b).

Although studies confirm the biologic plausibility of the BINT, rigorous human studies examining the consequences of these injuries, their recovery trajectory, and factors that determine their outcome are needed. Because of lack of information, adverse neurologic and

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behavioral changes in blast victims might be underestimated, and valuable time for preventive therapy or timely rehabilitation might be lost (Warden, 2006; Martin et al., 2008).

Penetrating Traumatic Brain Injury

Penetrating TBI is generally inflicted by munitions fragments, high-energy bullets, or other fragments generated by an explosion. In the recent warfare, penetrating TBI caused by secondary blast effects is only one of the elements of BINT. Penetration by a fragment or object depends on the energy of the projectile and the retardation caused by the fragment-tissue interaction. The retardation—which is a function of the shape of the object (the presented area), the angle of approach, and the properties of the tissue—determines the amount of energy transferred into the tissue, whereas the extent of damage depends on delivered energy (Sapsford, 2003). Projectiles with high available energy, such as fragments generated by an improvised explosive device, usually transfer large quantities of energy and cause strong stress waves and large temporary cavities (Yoganandan et al., 1997). The temporary cavities, lasting only a few milliseconds, expand fast, decreasing pressure to below atmospheric and sucking debris into the wound (Sapsford, 2003; Zhang et al., 2005b). A cavity's collapse is preceded by several smaller expansions and contractions of decreasing amplitude. The extent of damage to tissue in a nonelastic environment like the brain is estimated to be 10–20 times the size of the projectile.

Experimental Studies. Experimental studies on wound ballistics demonstrate pathophysiologic wounding properties of a penetrating brain injury distinct from those of the other types of head injury (Carey et al., 1990b; Soblosky et al., 1992; Torbati et al., 1992; Carey, 1995; Williams et al., 2006a; 2006b). If a missile penetrates a cerebral hemisphere without severe disruption of vital brain structures, the indirect effect of ordinary pressure waves, set up by the interaction of missile and tissue, may damage the brain stem respiratory nuclei and cause death (Carey, 1995). Thus, the possibility of fatal apnea is directly related to the missile energy of deposit in the brain. Moreover, it has been shown that although transmitted ordinary pressure waves might interfere with the reticular activating system in the brainstem and induce persistent coma, specific long-lasting neurologic defects from a missile wound generally result from direct missile damage to the cerebral cortex or cortical projections (Carey, 1995). The pathobiology of penetrating TBI also includes vasogenic edema around the missile wound track in the injured hemisphere (Carey et al., 1990a; 1990b); increase in ICP; decrease in cerebral perfusion pressure (Carey et al., 1989; Carey, 1995); widespread stretch injuries of blood vessels, nerve fibers, and neurons; and distortion and displacement of the brain (Finnie, 1993). Recent experimental studies (Williams et al., 2006a; 2006b; 2007) used a unilateral right frontal trajectory to induce survivable penetrating TBI of the frontal cortex and striatum and identified three distinct phases of injury progression. Phase I (0–6 hours), the primary injury, began with immediate (<5 minutes) intracerebral hemorrhage; maximal volumetric size developed at 6 hours after the trauma. In phase II (6–72 hours), the secondary injury, cells undergoing necrotic cell death and infiltrated neutrophils (24 hours) and macrophages (72 hours) formed a core lesion of degenerate neurons surrounding the injury track. The core lesion expanded into perilesional areas and reached maximal volume at 24 hours after the trauma. Phase III, delayed degeneration, developed 3–7 days after the trauma and involved neurogenic inflammation and degeneration of neurons and fiber tracts in structures remote from the core lesion, such as the thalamus, the internal capsule, the external capsule, and the cerebral peduncle (Williams et al., 2006a, 2007).

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Clinical Studies. Despite continuing efforts of the International Brain Injury Association, the Brain Injury Association of America, and other international and national surgical and neurosurgical associations, there is no consensus about the management of patients who have suffered brain injury caused by missiles and other penetrating objects. The lack of consensus could underlie apparent discrepancies in clinical studies concerning diagnosis, therapy, and rehabilitation of patients with penetrating TBI (Blissitt, 2006; No Author, 2001a, b; Pabuscu et al., 2003). For example, there are differing opinions about the usefulness of decompressive craniotomy, a method to convert the confined-space skull into an open one by removing part of the skull (Sahuquillo and Arikan, 2006); use of hypertonic saline solution vs mannitol in posttraumatic brain-edema treatment; aggressive vs less aggressive debridement of the wound (Taha et al., 1991; Levy, 2000; Tong et al., 2004); and treatments of CSF leaks, a frequent consequence of penetrating head wounds (Brandvold et al., 1990; Aarabi et al., 1998). Guidelines that have a sound scientific basis are necessary to achieve a consistent approach to the management of penetrating TBI patients.

Diffuse Brain Injury

As described above, movement of the brain caused by sudden acceleration followed by deceleration, in which the inertial effect depends on the brain mass and determines the extent of tissue deformation, has been identified as one of the most important mechanisms of diffuse brain injury (Ommaya and Gennarelli, 1974; Adams et al., 1989). In military settings, diffuse brain injury is often caused by tertiary blast effects (for example, a body flying through the air and hitting other objects), which then contribute to the complexity of BINT. Diffuse axonal injury, characterized by morphologic changes in axons throughout the brain and brainstem, has contributions from both primary and secondary injury mechanisms, and is recognized as one of the main consequences of nonmissile TBI leading to the diffuse degeneration of cerebral white matter (Adams et al., 1989). It is noteworthy that the distribution of the types of diffuse axonal injuries seen in BINT are substantially different from that of TBI of nonblast origin (Cernak et al., 2001b). The most common locations involve the brainstem, the cerebellum, gray matter–white matter junctions, and the internal capsule.

SEVERITY SCORING OF BLAST INJURIES AND TRAUMATIC BRAIN INJURY

Severity Scoring of Blast Injuries

The severity of injuries inflicted by explosive weaponry is usually scored by using the Abbreviated Injury Scale (AIS) or the Injury Severity Score (ISS). The AIS was first reported in 1971 for classification of anatomic injury from motor-vehicle collisions (Committee on Medical Aspects of Automotive Safety, 1971); it was not designed primarily to measure penetrating injury and high-velocity ballistic injuries. In an attempt to develop an improved injury-scoring system, the ISS was derived from the AIS and the Comprehensive Injury Scale, both of which were established to measure anatomic injury (Baker et al., 1974). The ISS correlated well with survival of the multiply injured blunt-trauma patient (Bull, 1978), but a similar relation for penetrating and war or gunshot injuries was not seen (Beverland and Rutherford, 1983) until the 1985 version of the AIS (American Association of Automotive Medicine, 1985). That was important not only for the improvement of injury scaling of blunt trauma but as an extension that made it possible to include penetrating injuries. The last revision of the AIS (AIS 2005) contains

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more than 2,000 injury descriptors, each of which can be localized to a small section of the body, if desired, by using precise methods incorporated into the scale (Gennarelli and Wodzin, 2006). Moreover, AIS 2005 includes new sections that cover blast and other nonmechanical injuries (Gennarelli and Wodzin, 2006).

The Red Cross Wound Classification (RCWC) was developed as a grading system for use under adverse conditions on the battlefield, scoring such wound features as degree of tissue damage, presence or absence of metallic fragments, and presence or absence of a cavity. Once scored, the wound can be further graded according to severity and typed according to structures injured; thus, wounds can be identified by their clinical significance (Coupland, 1992). However, there has been some discrepancy between the RCWC, routinely performed on the battlefield during combat operations in the former Yugoslavia, and clinical signs and outcomes of patients with blast injuries (Savic et al., 1993; 1995).

With regard to blast injuries, there is not an easily applicable and reliable scoring system. Experimental studies have often used the Walter Reed Army Institute of Research Blast Injury Subjective Score, which establishes blast-injury severity on the basis of the extent of lung damage (Jaffin et al., 1987; Mayorga, 1997) but does not take into account injuries in other organs or organ systems due to blast exposure. A pathology scoring system (PSS) for blast injuries (Yelverton, 1996) uses an alphanumeric measure of the severity of various lesions caused in animals by a blast wave, including those induced by secondary or tertiary effects, to arrive at a severity-of-injury index (SII) for each subject. That complex system correlates external lesion, injury grade, severity type, and severity depth or disruption of the injury with the presence or absence of some complications (such as pneumothorax, hemothorax, hemoperitoneum, coronary air, and cerebral air) and with the trauma outcome (nonfatal or fatal). A modified Yelverton scoring system has been helpful in some clinical studies (Cernak et al., 1999b).

Severity Scoring of TBI

Assessment of injury severity is of fundamental importance in the clinical management of patients with TBI and for developing novel diagnostic and therapeutic approaches. The Glasgow Coma Scale (GCS) has been the gold standard of neurologic assessment of trauma patients since its development by Teasdale and Jennett in 1974 (Teasdale and Jennett, 1974). Other TBI severity-classification systems grade single indicators, such as loss of consciousness (LOC) and duration of posttraumatic amnesia (PTA). The predictive value of those measures has been demonstrated (Dikmen et al., 1990; Levin et al., 1990; Levin, 1990; 1995; Sherer et al., 2008), but each may be influenced by factors unrelated or indirectly related to the severity of TBI, such as intoxication, sedation, and other treatments.

Glasgow Coma Scale

The GCS is used to determine the depth and duration of impaired consciousness and for continued assessment. It includes three independently measured components of behavior: eye opening, motor responsiveness, and verbal performance (Teasdale and Jennett, 1974).

- *Eye Opening***.** Spontaneous eye opening is most highly scored (“4”) and indicates active arousal mechanisms in the brainstem. Eye opening in response to speech, which is scored a “3”, is a response to any verbal approach and indicates functional cerebral cortex in

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processing information. Eye opening in response to pain is scored a "2", suggesting functioning of lower levels of the brain. The lowest score, a "1", is assigned to patients when there is no eye opening in response to speech or pain.

- *Motor Response*. The highest score, "6", is assigned when the patient can process instructions and respond by obeying a command (Fischer and Mathieson, 2001). In the absence of response to a command, a painful stimulus is applied. When the patient makes an attempt to remove the source of the painful stimulus—that is, the arm crosses the midline in such an attempt—a score of "5" is assigned. If the patient withdraws from the painful stimulus, a score "4" is assigned. Abnormal responses to painful stimulus, such as flexion or extension of the upper extremities, indicate more severe brain dysfunction. Decortication is manifested by adduction of the upper extremities with flexion of the arms, wrists, and fingers, whereas the lower extremities will extend and rotate internally with plantar flexion of the feet (a score of "3"). That response suggests lesions in the cerebral hemispheres or internal capsule. Decerebration is manifested with adduction and hyperpronation of the upper extremities, whereas the legs are extended with plantar flexion of the feet. Opisthotonus, a backward extension of the head and arching of the back, is also a manifestation of decerebration, damage extending from the midbrain to the upper pontine (a score of "2"). A score of "1" is assigned when the patient fails to respond to a painful stimulus.
- *Verbal Response*. Orientation—the patient's ability to know his or her identity (person), where he or she is (place), and the current year, season, and month (time)—is the first component tested. When the patient is oriented, the maximum score of "5" is assigned. In the case of confused conversation, a score "4" is given, and inappropriate speech is scored a "3". Incomprehensible speech that refers to moaning and groaning but without any recognizable words is scored a "2", and a score of "1" is assigned to patients without verbal response.
- *Overall Score*. The final GCS is derived as the sum of all scores. On that basis, TBI can be classified as mild (GCS≥ 13), moderate (GCS 9–12), or severe (GCS ≤ 8). To improve the sensitivity of the GCS and its prognostic value, Stein and Spettel (1995) developed a head-injury severity scale for closed TBI, defining five GCS intervals: minimal head injury (GCS = 15, no LOC or amnesia), mild head injury (GCS = 14, or 15 plus amnesia, or <5-minutes LOC, or impaired alertness or memory), moderate head injury (GCS = 9–13, or LOC ≥5 minutes, or focal neurologic deficit, severe head injury (GCS = 5–8), and critical head injury (GCS = 3–4)

The Mayo Classification System

Taking into account the unreliability of some TBI indicators and the incidence of missing or incomplete documentation in the medical records, the Mayo Classification System's aim was to take advantage of positive evidence regularly available in the medical records for each case (Malec et al., 2007). The system was proposed for use in retrospective studies and for estimating TBI severity in cases presenting postacutely for medical care or rehabilitation. The Mayo Classification System classifies TBI in three major categories: moderate-severe (definite), mild (probable), and symptomatic (possible).

Moderate-severe (definite) TBI includes patients manifesting one or more of the following criteria: death due to the TBI, LOC of 30 minutes or more, posttraumatic anterograde amnesia of 24 hours or more, a worst GCS full score in the first 24 hours of less than 13 (unless

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invalidated on review, for example, attributable to intoxication, sedation, or systemic shock), and the presence of one or more of intracerebral hematoma, subdural hematoma, epidural hematoma, cerebral contusion, hemorrhagic contusion, penetrating TBI (dura penetrated), subarachnoid hemorrhage, and brainstem injury.

Mild (probable) TBI includes patients without any criteria of moderate-severe (definite) TBI and with one or more of LOC momentary to less than 30 minutes, posttraumatic anterograde amnesia of momentary to less than 24 hours, and depressed, basilar, or linear skull fracture (dura intact).

Symptomatic (possible) TBI includes patients without any criteria of moderate-severe (definite) and mild (probable) TBI and with one or more of blurred vision, confusion (mental-state changes), daze, dizziness, focal neurologic symptoms, headache, and nausea.

Comparisons with traditional single-measure systems (such as LOC or PTA) and approximate calculations of sensitivity and specificity have indicated that the Mayo system classifies TBI severity with reasonable accuracy (Malec et al., 2007).

The Brief Traumatic Brain Injury Screen

The Brief Traumatic Brain Injury Screen (BTBIS) is a one-page paper-and-pencil questionnaire designed by the Defense and Veterans Brain Injury Center (DVBIC) to screen for TBI in soldiers (DVBIC, 2007; Schwab et al., 2007) (Figure 2.7). It begins with a few questions about basic demographics and deployment history over the preceding 2 years, which are followed by three questions designed to identify possible TBI. The first of those, question S3, inquires about any injuries received during deployment with checkboxes indicating blast, vehicular, bullet, falls, and “other” as categories of injuries. Question S4 asks about neurologic features of TBI, including alterations in consciousness and LOC that resulted from injuries identified by the previous question. Question S4 also includes the categories “having symptoms of concussion afterward” and “head injury”, which are not part of the definition of TBI; those were included to provide further description of the injury for clinicians. Finally, question S5 aims at identifying specific symptoms and problems that are thought to be possibly associated with a head injury or concussion. Generally, it takes about 3–4 minutes to complete the BTBIS.

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S3. Did you have any injury(ies) during your deployment from any of the following? (check all that apply)

1. Fragment
2. Bullet
3. Vehicular (any type of vehicle, including airplane)
4. Fall
5. Explosion (IED, RPG, land mine, grenade, etc)
6. Other specify:_____

S4. Did any injury you received while deployed result in any of the following? (check all that apply)

1. Being dazed, confused, or "seeing stars"
2. Not remembering the injury
3. Losing consciousness (knocked out) for less than a minute
4. Losing consciousness for 1-20 minutes
5. Losing consciousness for longer than 20 minutes
6. Having any symptoms of concussion afterward (such as headache, dizziness, irritability, etc)
7. Head injury
8. None of the above

S5. Are you currently experiencing any of the following problems that you think might be related to a possible head injury or concussion? (check all that apply)

1. Headaches
2. Dizziness
3. Memory problems
4. Balance problems
5. Ringing in the ears
6. Irritability
7. Sleep problems
8. Other specify: _____

* These are selected items from the instrument identified in the paper as the BTBIS. The screen was designed generally without reference to head injury or traumatic brain injury in order to encourage as wide a report of possible TBI as possible. Items not shown here are questions regarding personal identifying information, helmet type, and deployment history. The entire form fits on a one-page scannable form.

FIGURE 2.7 Brief Traumatic Brain Injury Screen.
SOURCE: DVBIC, 2007. Reprinted with permission from Lippincott Williams and Wilkins, 2008.

The Military Acute Concussion Evaluation

The Military Acute Concussion Evaluation (MACE) has been developed by the DVBIC as a tool for determining cognitive deficits due to mild TBI (DVBIC, 2006a, b). The major goals of the MACE are to confirm the diagnosis of mild TBI, and to provide further assessment data by using the Standardized Assessment of Concussion (McCrea et al., 1997), to record neurocognitive deficits. The MACE can be easily used by medics and corpsmen and can be administered within 5 minutes. The four cognitive domains tested are orientation, immediate memory, concentration, and delayed recall. The MACE is recommended for use in military theater at levels I, II, and III. It is recommended that beyond the use of the MACE other neurocognitive measures be implemented at Level III toevaluate the cognitive state of an injured service member comprehensively.

Severity Scoring of BINT

Because moderate, moderate-to-severe, and severe BINTs are often part of complex polytrauma, proper diagnosis of BINT should include both classification of blast injuries and severity scoring of the head injury. The most recent version of the AIS (AIS 2005) (Gennarelli and Wodzin, 2006) incorporates blast injuries and is regularly used by the US Army; the global scoring of all injuries can be accomplished with that scoring system. In hospitals calculation of the modified PSS SII (Yelverton, 1996; Cernak et al., 1999b) can give additional information that might be valuable for treatment strategies and outcome prediction. A combination of head AIS, as an anatomic measure, and the GCS, as a physiologic measure of brain-injury severity, is useful for initial estimation of brain damage.

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3

EPIDEMIOLOGY OF ADULT TRAUMATIC BRAIN INJURY

This chapter reviews the scientific literature on the epidemiology of traumatic brain injury (TBI) and on incidence, prevalence, severity, external causes, risk factors, mortality, case-fatality rates, and disability estimates among others. For purposes of this chapter, the papers reviewed were published in 1980 or later, focus on adults only, include incidence reports, and use established methods that resulted in a minimum of sources of bias and misclassification similar to criteria established by the committee for review of studies of long-term health outcomes. Review articles are included only as a source of reference.

Scales and Scoring Systems Used to Describe Traumatic Brain Injury

There are many classifications of TBI; for example, Knightly and Pulliam (1996) address the various components of TBI incurred in the military. As noted in Chapter 1, there are two basic types of head injury: closed and open. Closedhead injuries result from the concussive effects of such exposures as munitions explosions, falls, and deceleration injuries from vehicular crashes; the latter two have also been termed blunt-force injuries. Openhead injuries include those caused by penetrating forces, for example, from gunshots or shrapnel, or by impaling forces, such as from knives (see also Chapter 2).

Gross Severity of Traumatic Brain Injury

Different methods have been used in the last 3 decades to measure the magnitude of brain damage and to predict the outcome of injuries (see Chapter 2). The mostly widely used tool for measuring severity is the Glasgow Coma Scale (GCS), which was developed in 1974 by Teasdale and Jennett (1974)as a measure of neurologic deficits after TBI and was an important contribution to the standardization of early assessment of TBI. It uses a simple method of scoring three domains: eye-opening, verbal response, and motor function (Table 3.1) and yields a total score of from 3 (comatose or nonresponsive) to 15 (no deficits in any of the three domains). The interpretation of scores at the ends of the scale is relatively straightforward, but scores like 8 or 9 or 11 or 12 may be subject to judgment error. Although the GCS is relatively straightforward in its numeric results, the classification of severity has been inconsistent. Many incidence studies have classified severity according to GCS scores of 3–8, severe; 9–12, moderate; and 13–15, mild or minor (e.g., Kraus et al., 1984; Thurman et al., 1996; Langlois et al., 2003). Permutations of that approach are summarized in Table 3.2 (US studies) and Table 3.3 (non-US studies).

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It was originally intended that the GCS would be applied repeatedly during a patient's hospital course to monitor improvement or deterioration—during emergency transport, in the emergency department (ED), during intensive care, and throughout primary care. Because GCS scores have been reported in almost all recent studies of TBI severity, it is important to compare only readings taken at similar times after injury among studies. The most common time for determining the GCS score is 6 hours after injury, which is generally when the patient is in the ED. The GCS is subject to limitations when used on some patients, such as young children, people with extensive facial injuries that would preclude eye assessment, people subject to cross-language misunderstandings, and people who have been intubated or sedated on arrival at the ED. A major limitation of the GCS is the effect of intoxication. As many as 35 to 50% of adult civilian patients transported to the ED may be under the influence of alcohol (Jagger et al., 1984a), so its effect on the GCS score and its interpretation cannot be ignored. A study by Sperry et al. (2006), however, suggests that alcohol intoxication had little effect on the GCS.

Nell and associates (2000) introduced an extended version of the GCS (GCS-E) to address difficulties of its application to the mild forms of TBI (Table 3.1)A study by Drake and colleagues (2006) showed that the extended GCS is a useful tool for the prediction of symptoms connected with mild TBI. The GCS should not be confused with the Glasgow Outcome Scale (GOS) (Table 3.1). The GCS is a physiologic measure of consciousness and the GOS is a gross measure of complications or residual effects following severe brain injury (Jennett and Bond, 1975)

Other methods and instruments have been used as alternatives to the GCS, such as the Abbreviated Injury Scale (AIS) (see Chapter 2) and the International Classification of Diseases (ICD). Clinical measures—such as loss of consciousness (LOC) and duration of posttraumatic amnesia (PTA)—and computed tomography of brain lesions have also been used to assess TBI severity. Table 3.2 shows examples of TBI incidence studies conducted in the United States that used those measures. As can be seen there is no consistency in severity classification systems reflecting available clinical symptoms or evidence from neuroimaging. A review of popular injury scales can be found in the review by MacKenzie (1984).

Outcome Scores and Predictors

The literature is replete with attempts to predict TBI outcomes on the basis of measurements in the ED or soon after intensive care. One of the most commonly used measures is the GOS (Table 3.1) developed by Jennett and Bond in 1975 (1975). Although the intent of the GOS was to address severe TBI, it has been applied over the years to less severe TBI. It is acknowledged as a crude measure of medical (neurologic) complications and sequelae but has found favor as a quick and reliable indicator of outcome especially of severe TBI (Teasdale et al., 1998). The GOS is most commonly applied at 3, 6, or 12 months postinjury but can be used at any time after intensive care. Pettigrew and associates (2003) recently showed that the GOS can be successfully applied over the telephone. There are many other measures, but only the GOS is covered in this chapter to assess patient disposition at hospital discharge. Because the gross categories of the GOS have some limitations, an extended version (the GOS-E) was developed (Jennett et al., 1981); the GOS-E adds three categories to the GOS and has good inter-rater agreement.

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INCIDENCE OF TRAUMATIC BRAIN INJURY

Incidence is the number of newly diagnosed cases occurring in a defined period, usually expressed with reference to a base of 100,000 persons. An incidence study is one in which only newly diagnosed TBI cases in a specified period of time in a population of known size have been enumerated and are included in the study group. Some 30 population–based TBI incidence studies conducted in the United States have been published since 1980 (Table 3.4). Early studies were limited to counties (Kraus et al., 1984), cities (Cooper et al., 1983; Whitman et al., 1984), and states, such as Oklahoma, Massachusetts, Louisiana, and Alaska. National or subnational estimates of the incidence of TBI have recently been published from the Centers for Disease Control and Prevention (CDC) TBI surveillance system (Langlois et al., 2003) or from existing national administrative datasets (Langlois et al., 2006). Methods used for incidence studies have varied. For example, some earlier studies (e.g., Rimel, 1981; Kraus et al., 1984) relied on hospital or coroner records for case findings based on discharge codes, reviewed original institutional records, and abstracted pertinent data. Later studies used hospital discharge records and electronic files; in a few instances, a trauma registry was the source of data on TBI (Warren et al., 1995).

On the basis of the data available from those studies, the incidence of hospitalizations for TBI in the US is about 140/100,000 persons per year. If the highest reported rate (367/100,000) and the lowest reported rate (69/100,000) are excluded, the average rate of hospitalization for TBI (plus cases of immediately fatal TBI) in the United States is about 130/100,000 persons per year. Those estimates do not include ED-based studies, with rates of 444/100,000 (Jager et al., 2000) or 392/100,000 (Guerrero et al., 2000). The rates given in Table 3.4 represent three case-finding methods: hospitalized cases and those identified from medical-examiner records, hospital discharge records only, and trauma-registry files. The differences in case-finding approaches and other methodologic differences result in different rates.

Some 36 TBI incidence studies conducted outside the United States have been published since the middle 1970s, most coming from Europe and Australia (Table 3.5). As in the US studies, a wide variety of methods were used in TBI case definition and ascertainment methods. Even when ICD TBI codes were used in existing hospital electronic discharge files, the codes selected were not uniform. About half the incidence studies did not evaluate TBI severity. Therefore, it is difficult to synthesize findings from the non-US studies.

Time Trends in Incidence

Few incidence studies have collected data beyond a single year or two. MacKenzie and associates (1990) reported an increase in TBI incidence in Maryland from 1979 to 1986. There did not appear to be any remarkable changes in TBI identification procedures in the state's database, and only patients admitted to the state's 56 acute-care nonfederal hospitals were counted. Using the US National Hospital Discharge Survey, a yearly survey sampled in such a way as to be representative of the US general population, Thurman and Guerrero (1999) reported a 51% decline in incidence from 1980 through 1995. The change over that period was from 199/100,000 to 98/100,000. They noted that the TBI-associated death rate also declined, possibly because of the preventive measures associated with motor-vehicle crash outcomes. The authors noted also that the greatest change in hospitalization rates was in those with mild TBI; that suggested a change in hospital admission practices.

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Time-trend studies of incidence are rare in Europe and nonexistent in Asia. Engberg and Teasdale (2001), in an analysis of 1979–1996 data from Denmark, reported an overall decline of 41% in the rate of hospitalization for TBI. The percentage decline varied with ICD code. The authors speculate that the decreases may be explained by changes in hospital admission practices and the possible effect of national prevention programs. Kleiven and associates (2003) observed a varied change in incidence in Sweden from 1987 to 2000: persons over 85 years old appear to have experienced an increase in TBI rates and younger persons a decrease.

Mortality

The most recent estimates in four US reports indicate an average of about 50,000 deaths each year with TBI-related causes (Table 3.6). The most recent reported TBI mortality in the United States is 17.5/100,000 persons per year (Rutland-Brown et al., 2006). Sixteen incidence reports provide mortality data on subsets of the US population. The years in question are from 1974 through 2003, and the rates vary from 17/100,000 per year to 30/100,000 per year. The large US studies are based on data from the National Center for Health Statistics, and the rates for the latest years are tightly clustered from 17/100,000 per year to 21/100,000 per year. It should be kept in mind that methods of collecting mortality data vary somewhat, but the rates in most studies are based on death-certificate review.

TBI mortality in non-US countries varies much more widely than that in the US (Table 3.7). The lowest rate reported—5.2/100,000 of populations in Aquitaine, France—reflects only inpatient deaths (Masson et al., 2001). Low rates have also been reported in northeast Italy, South Australia, and Norway. The highest TBI-death rates on record are in Johannesburg, South Africa (81/100,000), and Hualien County, Taiwan (82/100,000) (Nell and Brown, 1991; Chiu et al., 1997).

Prevalence of Traumatic Brain Injury (Disability)

Prevalence reflects the total number of cases of TBI at a specified point in time and includes all newly diagnosed patients plus those persons with residual physical and neuropsychologic problems. It should not be confused with incidence. Prevalence is a measure of the cumulative occurrence of TBI in the population at the point or period when measured. It is difficult to determine the exact prevalence of TBI in the United States, but there are estimates of disability—physical, mental, or social impairment—as a result of TBI. The literature on TBI disability is large and is based on occurrence of disability in a group of persons who have survived and might not be representative of the entire population. For purpose of this chapter, two recent US studies are highlighted because their findings were based on original incidence cohorts with excellent followup methods to ascertain outcomes.

From 1996 to 1999, 2,771 Colorado residents 16 years old or older were discharged alive from an acute-care hospital after a diagnosis of moderate or severe TBI (Whiteneck et al., 2004). After multiple attempts at contact, 1,591 were located and responded to structured interviews on a variety of outcomes. Information was sought 1 year after injury on health-service use, the Functional Independence Measure, the Craig Handicap Assessment and Reporting Technique (CHART), and a single question on quality of life. The study authors noted that 65% had problems in cognition (any symptom); 71% used at least one service after injury; 15–37% had activity limitations, depending on the type of activity; and 24 % failed to return to work. With

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regard to CHART components, 16% were impaired or disabled; and 29% reported less than good quality of life. The authors concluded that "substantial percentages of people hospitalized with TBI in a population-based sample reported a variety of problematic outcomes at 1 year postinjury." It is noteworthy that the problems experienced by members of that injury cohort were in many cases similar in all levels of initial TBI severity.

The second study of the incidence of disability was a South Carolina population-based prospective cohort study reported by Pickelsimer et al. (2006). Followup was completed at 1 year after injury with such outcome measures as service needs, psychosocial health, health-related quality of life, functional status, TBI-related symptoms, employment, and life satisfaction. Outcome findings included one or more functional limitations in about 47% of the subjects, unmet service needs in about one-third (35%), and dissatisfaction in quality of life in about one-third (35%). In a second report of that study, Selassie et al. (2008) used the same population sample and outcome measures to estimate the incidence of long-term disability in the United States. The researchers concluded that among the 288,009 survivors hospitalized for TBI in 2003, almost 125,000 (over 43%) had long-term disability. The disability rate varied by age and sex; it was higher in females than in males and was highest in people who fell and in those with self-inflicted injuries.

Information on annual disability does not quantify the cumulative prevalence of TBI disability or impairment in the population. If 43% of a hospital-discharged TBI population sustains some form of disability or impairment in 1 year, the question remains, how much of the total population is disabled or impaired from TBI sustained in earlier years? Thurman and colleagues (1999) attempted to estimate that number by using the US National Hospital Discharge Survey data to approximate incidence and then classified the data by TBI severity by applying the computer algorithm known as ICDMAP-90 developed by MacKenzie et al. (1989b). The probability of disability was estimated for each level of severity by using outcome findings on disability from the Colorado state TBI registry and estimation parameters developed by Kraus and McArthur (1996). On the basis of that model, CDC estimated that 5.3 million United States citizens (2%) were living with TBI-related disability in 1996. If that proportion is applied to the 2007 US population of over 301 million people, then just over 6 million people are living with the effects of TBI, and 2 million people have unmet health-service needs.

BRAIN INJURY SEVERITY

As discussed above, LOC is the most common measure used for evaluating brain injury severity and the most widely used tool for LOC is the GCS. Problems that arise in comparing the GCS measured in different places come from differences in timing. For example, intubation and sedation of the brain-injured patient during transport to the ED will obviously affect the person's verbal and motor abilities and eye responses. Differences in timing in the administration of any measurement tool can be critical so Teasdale and Jennett suggested that the GCS be applied at six hours post-injury. However, because a patient's injury may require ED procedures like intubation and sedation or acute surgical intervention, repeat measures may be necessary, often minutes or hours apart. Hence there does not appear to be an ideal window that is the best for the GCS, but, if it is to have any predictive quality, it should be applied early in the clinical management of TBI.

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Severity Distributions

The distribution of severity of brain injury as assessed by the GCS (or other parameters) is shown in (Table 3.8). Of the more than 60 population based incidence studies published worldwide since 1980 only 22 address the degree of TBI severity in the study populations; 10 are from the US and 12 from non-US countries. Most studies used the GCS to evaluate brain injury severity but some also used the AIS. The majority of hospital-admitted brain injuries are classified as "mild" (generally, a GCS score of 13 to15 or AIS of 1 or 2). However, the mild category is viewed differently by different researchers some of whom use mild to describe any GCS score above 7 while others refer to GCS scores above 8, above 10, above 13, or 15 only (Kraus and Chu, 2004). Studies published in the 1980's, with the exception of the report from Oklahoma, showed a ratio of mild to moderate to severe of about 8:1:1.

With one or two exceptions almost all studies in the US show lessthan 20% of patients admitted to a hospital are in the severe TBI range, and mild TBI is diagnosed60 % or more of the time. However, researchers outside the US report severity distribution proportions at even more consistent levels. A study by Hillier et al. (1997) evaluated TBI severity using three different measures: the GCS, LOC, and PTA; results were very similar, which provides support to the acceptance of severity classification when each of those measures is used. Severity distribution findings from non-US studies (Table 3.8) are similar to those from the US with a ratio of mild to moderate to severe of 7:1:1. The high percentage of severe TBI admissions for Northeast Italy (Baldo et al. 2003) and the Romagna region of Italy (Servadei et al. 2002) may reflect the referral practice of the acute medical care treatment institutions involved.

RISK FACTORS FOR TRAUMATIC BRAIN INJURY

Several risk factors have been examined in connection with the incidence of TBI: age, sex, ethnicity, and socioeconomic status. Data on age and sex in TBI can be found in 60 of the 66 papers reviewed (Tables 3.9 and 3.10). Although the papers do not necessarily group ages similarly, findings are remarkably consistent; the age group with the highest incidence of TBI is 15–24 years. In some reports, age groups at highest risk depend on TBI severity. For example, the very young (0–4 years old) and the very old (at least 85 years old) present to an ED with a brain injury most frequently, whereas those 15–24 years old and over the age of 65 years are hospitalized with TBI most frequently. The age-specific rates tend to reflect differences in exposure, particularly to motor-vehicle crashes and falls. Males are at greater risk for TBI than females at all ages in all incidence studies. Every report that gives data on sex-specific incidence shows that males have much higher TBI rates than females, and the ratio of male incidence to female incidence often exceeds 2. In one report (Nell and Brown, 1991), the incidence ratio of males to females exceeded 4 in both blacks and whites in Johannesburg, South Africa. The researchers posit that men in Johannesburg are involved in much higher levels of aggressive activities than women in the same city. The sex-specific mortality ratio is about 3.5:1, strongly indicative of more severe injuries among males (Adekoya et al., 2002).

The US TBI death rate in 1989–1998 averaged 27/100,000 in American Indians and Alaskan Natives, 25/100,000 in blacks, and 20/100,000 in whites (Adekoya et al., 2002). The nonfatal-TBI hospitalization rate in 1997 (based on a 14-state surveillance system) was 74/100,000 in blacks, 75/100,000 in American Indians and Alaskan Natives, and 63/100,000 in

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whites (Langlois et al., 2003). ED incidence studies of TBI show similar results, albeit often lacking complete racial and ethnic categories. For example, the report by Jager and associates (2000) shows the rate of ED-treated TBI in blacks as 582/100,000 and the rates in whites and all others as 429/100,000 and 333/100,000, respectively. Data from the US National Health Interview Survey for 1991 (Sosin et al., 1996) show that whereas ED TBI rates were higher in whites than in blacks or Hispanics, the TBI hospital-admission rates were the opposite, that is, lower in whites than in other race and ethnic groups. Similarly, Nell and Brown (1991), in a 1986 TBI study in Johannesburg, South Africa, reported an incidence 3.3 times higher in blacks, 1.9 times higher in Asians, and 2.7 times higher in coloureds (mixed race) than in whites.

Higher risk of TBI is often associated with lower socioeconomic status (SES) because there might be increased exposure to physically demanding or unsafe employment settings, increased exposure to violence, or increased exposure to less well-maintained residences or older vehicles without newer safety features (Hoofien et al., 2003). In the United States, families at the lowest income levels have been shown to incur the highest numbers of injuries of all types on a per capita basis (Collins, 1990). That was found to be true for TBI in a study of San Diego County residents (Kraus et al., 1986), in two Chicago communities (Whitman et al., 1984), and in Rhode Island (Fife et al., 1986). The San Diego County study demonstrated that the link between injury and low SES was not modified when the analysis controlled for race or ethnicity.

Two more recent studies have demonstrated the link between the incidence of TBI and race or SES. Selassie et al. (2003, 2004) in a large cohort study of TBI in South Carolina showed that the disposition of TBI patients from the ED might be influenced by insurance status and other factors. Furthermore, black females and the uninsured were less likely to be hospitalized for TBI after adjustment for important confounders. However, Yates et al. (2006) determined hospital TBI "attendance" rates in an ED in a large UK population from 1997 to early 2003 by using the Index of Multiple Deprivation and noted that the highest TBI attendance rates were in groups with the lowest SES.

Alcohol consumption can disrupt brain activity. Intoxication greatly increases various risks, including risks posed by motor-vehicle operation and the risk of self-inflicted injury and assault (e.g., Waller et al., 1986; Modell and Mountz, 1990). Also, intoxication can complicate diagnosis in the ED by increasing LOC independently of brain-injury severity (e.g., Jagger et al., 1984a). The association between blood alcohol concentration (BAC) and risk of TBI is well established for all external causes, such as motor-vehicle crashes, violence, and even falls. One of the earliest incidence reports on TBI and alcohol involvement was by Rimel (1981), who showed that 72% of patients identified in a central Virginia TBI databank had positive BAC rates on admission and 55% were legally drunk (BAC, 0.10% or higher). Kraus et al. (1989) reported in a TBI incidence study of San Diego County residents in 1981 that 49% of those who were tested for BAC had a BAC of 0.10 % or higher (which is either an offense itself or presumptive evidence of driving under the influence). Langlois et al. (2003), reporting on a 14-state TBI surveillance system in 1997, found that 43% of those (including pedestrians) who sustained TBI in motor-vehicle crashes had a BAC of 0.10% or higher; the percentages of those who sustained TBI in falls and assaults were 7% and 28%, respectively. Warren et al. (1995), in a study of TBI in Alaskan residents, reported that almost 67% of those tested had a BAC of 0.10% or higher.

Findings like those are not peculiar to the United States. A few non-US TBI incidence studies show evidence of alcohol use. Chiu and colleagues (2007) found that 15% of adults who sustained TBI in 2001 in Taipei City, Taiwan, used alcohol before the injury incident compared

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with 42% in Hualein County in the southern part of Taiwan. Researchers in Spain (Vazquez-Barquero et al., 1992) reported that 55% of males and 40% of females with TBI who presented for admission were intoxicated. Similarly, positive BAC rates were reported by Nestvold et al. (1988) and Ingebrigtsen et al. (1998). Simpson and co-workers (1981) reported that among those who died of TBI in New South Wales and were tested, 44% of motor-vehicle drivers, 39% of suicides, 27% of people who sustained TBI in falls had BAC of 80 mg% or higher. The percentages of people who were tested for BAC in the last four reports were not reported.

External Causes of Traumatic Brain Injury

Only about half the 66 US and non-US studies reporting the incidence of TBI give details on the exposures that led to it. Data from those studies (Tables 3.11 and 3.12) suggest that the most frequent exposure associated with brain injury is transportation. That category includes automobile and truck occupants, bicycles and motorcycle riders, and pedestrians hit by vehicles and, less frequently, aircraft, watercraft, and road farm equipment. One precaution in discussing reported external causes is that the specific components of each of the general categories are not always uniform. For example, TBI stemming from bicycle–motor-vehicle collisions may be classified as “motor vehicle” or “sports or recreation”, depending on the inclination of the researcher. As can be seen from Tables 3.11 and 3.12, the distributions of those gross external causes can vary widely among studies, but they do illustrate vast differences within a general cause. For example, in the two US ED-based studies (Jager et al., 2000; Guerrero et al., 2000), the most important exposure reported is falls, compared with hospital-based studies, in which transportation is the most frequent cause of brain injury. But in two US studies and the study in South Africa, the most frequently reported external cause is violence (which includes the use of firearms and self-inflicted injury); in these studies, incidence was determined on the basis of inner-city populations. An analysis by Adekoya (2002) in the United States reported that the leading cause of TBI deaths was violence, especially related to firearms. Falls are also an important cause of TBI in the United States. Recent studies reported by Rutland-Brown (2006) in the United States and Ingebrigtsen (1998) in Norway show falls as the leading cause of TBI. Additional important exposures involve sports and recreational activities. Misclassifications are likely, however; for example, sports-related events may account for up to 10% of TBI deaths but might be reported as falls or as being struck by an object (Whitman et al., 1984). Reports from Alaska (Warren et al., 1995) and Australia (Tate et al., 1998) show sports and recreation activities account for one-fifth to one-fourth of TBI hospital admissions.

Military Exposures

Although there is ample literature on injury in military populations (e.g., Smith et al., 2000), only three population-based TBI incidence studies could be located. McCarroll and Gunderson (1990) published a report on TBI hospitalization rates in the US Army. The database used was the US Army Patient Administration Systems and Biostatistics Activity for fiscal years 1983–1987. The number of active-duty personnel was obtained from the Defense Manpower Data Center. ICD-9 codes 800, 801, 850, 851, 852, 853, and 854 were used to identify hospital-admitted TBI patients. Incidences per 100,000 persons were derived by age group, sex, and race. About 2,500 patients were admitted each year over the 5-year study period. Rates of concussion and intracranial injury were somewhat higher in males than in females, but the reverse was

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observed in some years. The investigators found that 10% of the TBI patients had alcohol or drug involvement, and 97% of the alcohol related-TBIs were in males.

Ommaya and associates (1996) evaluated TBI incidence in the US military medical system. Records of discharges from military facilities and private facilities reimbursed by the military for fiscal year 1992 were reviewed for TBI admissions. Medical records of persons with a head-injury diagnosis—ICD-9-CM codes 800–801, 803–804, and 850–854—were identified. ICDMAP (MacKenzie et al., 1989b) was used to convert ICD codes to AIS values. The investigators reported an incidence of 21 (female beneficiaries) to 231 (male active-duty) per 100,000 of population by age group. TBI admission rates were higher in active-duty males 15–17 years old and 18–24 years old. The most common diagnosis was intracranial injury in military hospital admissions and frequently involved firearms. Falls and motor-vehicle crashes accounted for over 62% of the admissions, and fighting 10%. Case-fatality rates (CFRs) ranged from 0% for parachuting to 41% for firearms-related injury. Details on injury severity were not highlighted.

Ivins and associates (2006) studied rates of TBI hospitalization of active-duty US Army personnel in 1990–1999. The data source was the Standard Inpatient Data Record database. TBI was identified on the basis of at least one IDC-9-CM code of 800–801, 803–804, and 850–854 in the medical record. ICDMAP-90 was used to assign AIS severity scores for each diagnosis. When there was a lack of information, such as LOC, severity of the TBI was assigned by using criteria developed by the American Congress of Rehabilitation Medicine. Rate ratios were used to compare the incidence of TBI hospitalizations in the Army with the incidence in US civilians 17–49 years old. The overall TBI hospital admission rate in fiscal year 1990 was 248/100,000 active-duty personnel. The rate in 1999 was 62/100,000, 75% lower. TBI incidence declined in each of the three severity classes, but the largest decline in admission rates was in those who had a diagnosis of mild TBI. Overall admission rates declined equally in males and females and in all age groups. There was little change in rates of TBI hospitalization of military active-duty personnel treated in civilian hospitals during the same period. The researchers concluded that the basis of the dramatic decline in rates was effective injury-prevention measures, such as stricter drug- and alcohol-abuse policies, and changes in the Army population; and that changes in hospital admission policies most likely contributed to the decrease in rates of hospitalization for mild TBI.

RECURRENT TRAUMATIC BRAIN INJURY

Researchers at the Mayo Clinic (Annegers et al., 1980) were among the first to measure the relative risk (RR) of TBI in those with a previous brain injury. They estimated that the risk of a second TBI in those with an earlier TBI was about 3 times the risk of TBI in the general population without such a history. The RR of recurrent TBI given any initial head injury increased with age, and the RR of a third TBI given a second head injury was 8–9 times that of an initial head injury. Jagger et al. (1984b) observed that 31% of their TBI patients reported a previous hospitalization for a head injury. Nestvold and associates (1988) reported that 17% of 465 patients admitted to three hospitals in Akershus County, Norway, had reported an earlier head injury, and about one-fourth of those reported more than one previous TBI. Salcido and Costich (1992) called attention to some possible effects of repeat TBI, including psychosocial aspects and the course of a second rehabilitation. Ruff and co-workers (1990), Kreutzer and co-

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workers (1990), and Corrigan (1995) reviewed the literature on TBI and recurrent injury and showed a strong association with alcohol abuse. Closely related to repeat TBI is what has been called the "second-impact syndrome", in which a repeat mild TBI was catastrophic or even fatal (Kelly et al., 1991).

Gronwall and Wrightson (1975) concluded that the effects of concussion might be cumulative especially in sports, in which populations may be easily monitored. Recurrent head injury in sports has been the subject of several case reports and case-series studies (e.g., Kelly et al., 1991; Cantu and Voy, 1995). Their findings of risks posed by recurrent TBI have prompted recommendations on when players can return to games in the event of even a minor concussion (CDC, 1997).

TRAUMATIC BRAIN INJURY AND SHORT-TERM OUTCOMES

One outcome of TBI is death. Whereas mortality is an ideal measure of the magnitude of severity of TBI in the general population, the case fatality rate (CFR) after hospital admission is a measure of the immediate gross consequences of brain injury. The CFR has been used for decades as an indicator of hospital quality of care, but its use is subject to biases as described below.

Case-Fatality Rates

CFR data are available from 15 US population-based incidence studies (Table 3.13). They range from 4.4/100 hospitalized patients in Maryland (MacKenzie et al., 1989a) to about 25/100 in the Bronx, New York (Cooper et al., 1983), and 23/100 in Oklahoma (Oklahoma State Department of Health, 1991). The range in rates may reflect gross differences in hospital patient-admission practices. That is, hospitals that admit a high proportion of patients with severe brain injury would be expected to have higher CFRs than hospitals that admit a large proportion of patients with mild brain injury, who are less likely to die. CFRs in the most recent reports in the United States show the effect of changes in hospital admission practices of the last decade: fewer of the mildly head-injured persons were admitted.

Table 3-14 summarizes CFR data from outside the United States. The rates in the 15 studies range from 0.8/100 hospitalized patients in a report from South Australia (Badcock, 1988) to 30/100 in a county in Denmark (Engberg and Teasdale, 2001); the latter CFR represented only hospital-admitted patients with ICD-9-CM codes 850–854. The very low rate in South Australia may reflect the fact that over 90% of the patient cohort admitted to the hospitals in the study region had mild TBI. The CFR in severe-TBI patients in the study was 55%, which is comparable with rates in other studies that focused on severe-TBI patients. Discounting the single high CFR from Denmark, all remaining rates are less than 10/100 admitted patients.

Occasionally, a total or general CFR appears in the literature (e.g., Servadei et al., 2002a). Such a rate would reflect both in-hospital and prehospital deaths and express the risk of death from the moment of injury to hospital discharge. It is often 2 or 3 times the in-hospital CFR. Examples are found in Kraus et al. (1984), Vazquez-Barquero et al. (1992), and Tiret et al. (1990).

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Disposition at the End of Acute Care

As previously noted, one of the scales used to assess early outcome after hospitalization for TBI is the GOS. The GOS is a crude indicator of medical (neurologic) complications or of residual effects at the time of discharge from a primary treatment center. The major difficulty with the GOS is its inability to classify patients properly because of the lack of specific criteria that separate severe from moderate and moderate from the good-recovery categories. Good recovery does not mean, nor was it ever intended to mean, complete recovery, and, as noted above, Jennett (1981) devised an extended version of the GOS (GOS-E) to account for the insensitivity of the scale to some changes in functional ability, especially in the moderate and severe categories.

The large number of population-based TBI incidence studies might suggest the availability of much more information on the GOS as an early hospital-discharge tool, but only seven of the 66 studies (US and non-US) reported on the scale. Rimel (1981) observed that 69% of TBI patients had a “good recovery” at the time of discharge. The highest percentage of persistent vegetative state was also reported in that study. Almost all other studies in Table 3.15 had a rate of good recovery of 75% or higher. The one exception is the study by Masson (2003), in which only 18% of patients were discharged with a good recovery; their study population, however, consisted of only patients admitted to the hospital with severe TBI.

SUMMARY

Almost all the incidence studies had shortcomings, and that should be considered in drawing conclusions. No two published studies are identical in methods. However, many studies have used reasonable methods to identify patient cases, defined and measured the populations that gave rise to the patients, used acceptable methods in identifying patients in treatment facilities or in administrative datasets, defined TBI (and severity levels) in reasonable ways, classified exposures that gave rise to the injuries in ways that make sense, recorded basic descriptive information about patients in uniform formats, and, in longitudinal studies, followed patients for outcomes by using acceptable methods to reduce losses and used accepted outcome instruments. Thus, we can learn a great deal about the epidemiology of TBI and use that knowledge to help in designing prevention strategies.

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TABLE 3.1 Glasgow Coma Scales and Glasgow Outcome Scales

Glasgow Coma Scale[a]		**Glasgow Coma Scale-Extended**[b]		**Glasgow Outcome Scale**		**Glasgow Outcome Scale-Extended**[c]	
Ability Assessed	Points	Memory Assessed	Points	Condition	Points	Condition	Points
Eye-opening		Amnesia		Dead	1	Dead	1
Not open	1	>3 mo	0	Vegetative state	2	Vegetative state	2
To pain	2	31–90 days	1	Severely disabled	3	Lower severe disabled	3
To speech	3	8–30 days	2	Moderately disabled	4	Upper severe disabled	4
Spontaneous	4	1–7 days	3	Good recovery	5	Lower moderate disabled	5
Verbal response		3–24 h	4			Upper moderate disabled	6
Silence	1	0.5–3 h	5			Lower good recovery	7
Sounds	2	<30 min	6			Upper good recovery	8
Nonsense	3	No amnesia	7				
Confused	4						
Motor response to pain							
No response	1						
Arm extension	2						
Arm flexion	3						
Withdrawal	4						
Localizing	5						
To command	6						

[a]Source: Jennett and Teasdale, 1981.
[b]Source: Nell et al., 2000.
[c]Source: Jennett et al., 1981.

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TABLE 3.2 US TBI Incidence Studies: Case identification, data source, and TBI severity scoring

Reference	Year(s) of Data	Location	Case Definition and Data Source	TBI Severity Criteria and Scoring
Annegers et al., 1980	1935 to 1974	Olmstead County, MN	Record linkage with head injury, with concussion, with LOC, PTA, neurological signs of brain injury or skull fracture concussion, with LOC, PTA, neurologicsigns of TBI	Fatal: (< 28 days); Severe: intracranial hematoma, contusion or LOC > 24 hours, or PTA > 24 hours; Moderate: LOC or PTA 30 minutes to 24 hours, skull fracture, or both; Mild: LOC or PTA < 30 minutes without skull fracture
Klauber et al., 1981	1978	San Diego County, CA	ICDA-8 Codes 800, 801, 804 806, and 850-854 with hospital admission diagnosis or cause of death with skull fracture, LOC, PTA neurological	GCS of 3, 4-5, 6-7, 8-15
Rimel, 1981	1977 to 1979	Central Virginia	CNS referral patients with significant head injury admitted to neurosurgical service unit. Pre-hospital deaths from medical examiner	GCS (3-5, 6-8, 9-11, 12-15); severe = < 8; moderate = 9-11; mild = 12-15
Jagger et al., 1984b	1978	North Central Virginia	Patients within defined service area with overnight stay, and documented head injuries	Not reported
Kraus et al., 1984	1981	San Diego County, CA	Physician-diagnosed physical damage from acute mechanical energy exchange resulting in concussion, hemorrhage, contusion, or laceration of brain	Modified GCS: severe = < 8; moderate = 9-11; plus hospital stay of 4-8 hours and brain surgery, or abnormal CT, or GCS 9-12; mild = all others, GCS 13-15
Whitman et al., 1984	1979 to 1980	Inner city Chicago and Evanston, IL	Any hospital discharge diagnosis of ICD-9-CM 800-804, 830, 850-854, 873, 920, 959.0. Injury within 7 days prior to hospital visit and blow to head / face with LOC, or laceration of scalp or forehead	1) Fatal; 2) Severe = intracranial hematoma, LOC /PTA > 24 hours contusion; 3) Moderate + LOC or PTA 30 minutes to < 24 hours; 4) Mild + LOC or PTA < 30 minutes; 5) Trivial + remainder
Fife et al., 1986	1979 to 1980	Rhode Island	All admissions to Rhode Island hospitals Professional Activities Study (PAS) using ICD-9 codes 800-801.9, 803-804.9, 850-854.9	Severity not evaluated
Fife, 1987	1977 to 1981	US	US National Health Interview Survey translated rates ICD codes 800.0-801.9, 803.0-803.9, 850.0-854.9	Severity not evaluated

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Reference	Year(s) of Data	Location	Case Definition and Data Source	TBI Severity Criteria and Scoring
MacKenzie et al., 1989a	1986	Maryland	ICD-9-CM codes 800, 801, 803, 804, 850-854	ICDMAP - converts ICD codes to Abbreviated Injury Severity Scores
MacKenzie et al., 1990	1979 to 1986	Maryland	ICD-9-CM codes 800, 801, 803, 804, 850-854	ICDMAP - converts ICD codes to Abbreviated Injury Severity Scores
Fuortes et al., 1990	1984 to 1986	Iowa	State central head injury registry of hospital discharge abstracts	Not reported
Oklahoma State Department of Health, 1991	1979 to 1986	Oklahoma	Hospital discharge codes ICD-9-CM 800.0-800.9, 801.0-801.9, 803.0-803.9, 804.0-804.9, 850.0-850.9, 851.0-851.9, 852.0-852.9, 853.0-853.9, 854.0-854.9, 905.0, 907.0. Excluded ED visits, ME probable cause of death for TBI	AIS 1 = minor AIS 2 = moderate AIS 3 = 3-5 = severe
Cooper et al., 1983	1980 to 1981	Bronx, NY	Hospital / ED logs and ICD-9-CM codes 800-801, 803-804, 850-854	Not reported
Schuster, 1994	1989 to 1991	Massachusetts	State vital statistics mortality file ICD-9; codes 800-802, 803-804, 850-854, 873 State uniform hospital discharge data set ICD-9 CM codes 800-801,803-804, 850-851	Not reported
Warren et al., 1995	1991 to 1993	Alaska	State Trauma Registry ICD-9-CM codes 800-804, 850-854, 950-954	Not reported
Thurman et al., 1996	1990 to 1992	Utah	Discharge date from all Utah acute care hospitals and state vital records using ICD-9-CM codes 800.0-801.9, 803.0-804.9, and 850.0-854.1 in any primary or secondary data fields	1) Initial GCS: Severe = $\leq$ 8; Moderate = 9-12; mild = 13-15; 2) Demonstrated intracranial traumatic lesions; 3) Focal abnormalities on neurological examination
Diamond, 1996	1988 to 1993	Virginia	All ED treated patients from Virginia Brain Injury Central Registry including hospital admitted ICD-9-CM codes 850.0-854.1, 800.0-804.9, 348.1, 900.0-900.9, 950.0-951.9	Severity not evaluated
Gabella et al., 1997a	1990 to 1993	Colorado, Missouri, Oklahoma, Utah	Hospital discharge data for all state hospitals or healthcare providers	No severity data reported

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Reference	Year(s) of Data	Location	Case Definition and Data Source	TBI Severity Criteria and Scoring
Gabella et al., 1997b	1991 to 1992	Colorado	Colorado surveillance system of hospitalized and fatal TBI using ICD-9-CM codes 800, 801, 803, 804, 850-854	ICDMAP using as many as 5 ICD discharge diagnoses. Severe TBI = died or ISS > 9
Sosin et al., 1996	1991	US	Self-reported data from US National Health Interview Survey Injury Supplement. Mild and moderate brain injury defined as loss of consciousness in previous 2 months	Severity not evaluated
Thurman and Guerrero, 1999	1980 to 1995	US	All hospital discharge records with one or more ICD-9-CM code(s) of 800.0-801.9, 803.0-804.9 or 850.0-854.1 from the National Hospital Discharge Survey	ICDMAP used to convert ICD codes to approximate Abbreviated Injury Scale Scores. 1-2 = mild; 3 = moderate; 4-6 = severe
Jager et al., 2000	1992 to 1994	US	Same ICD codes as Thurman et al. 1996; identified from US National Hospital Ambulatory Medical Care Survey	Severity not evaluated
Guerrero et al., 2000	1995 to 1996	US	All visits to emergency departments with same ICD codes as Thurman et al. 1996; identified from US National Hospital Ambulatory Medical Care Survey	Severity not evaluated
Schootman et al., 2000	1993	Iowa	Hospital discharge data ICD-9 codes 800-801, 803-804, 850-854 [capture - recapture method] plus death certificates	No severity data reported
Langlois et al., 2003	1997	14 US states	State TBI surveillance projects. Deaths excluded, cases identified as ICD-9-CM 800.0-801.9, 803.0-804.9, 850.0-854.1, 959.01 plus evidence of LOC, PTA, skull fracture, etc.	GCS $\leq$ 8 = severe; 9-12 = moderate > 12 no brain lesions > 12 with brain lesion > 12 no cat. done
Langlois et al., 2006	1995 to 2001	US	ED visits from National Ambulatory Care Survey ICD-9-CM codes 800-801, 803-804, 850-854, 959 Hospitalizations: National Hospital Discharge Survey, same as ICD codes as above Deaths multiple cause of death taken from US National Vital Statistics System [some double counting was probable]	Not evaluated
Selassie et al., 2004	1996 to 2001	South Carolina	Statewide surveillance of TBI related hospitalizations. Used ICD-9-CM codes as in Langlois, 2003	Mild = AIS 1-2, Moderate = AIS 3, Severe = AIS 4-5

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Reference	Year(s) of Data	Location	Case Definition and Data Source	TBI Severity Criteria and Scoring
Texas Department of Health, 2004	1998	Texas	Texas Trauma Registry and Bureau of Vital Statistics ICD-9 codes 800-801, 803-804, 850-854	GCS used but not reported
Rutland-Brown et al., 2006	1995 to 2001	US	Update from Langlois et al. 2003, see this for case ID	See Langlois 2003

NOTE: AIS = Abbreviated Injury Scale, CA = California, CNS = central nervous system, CT = computed tomography, ED = emergency department, GCS = Glasgow Coma Scale, ICD = International Classification of Diseases, ICDA-8 = International Classification of Diseases, Eighth Revision, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, ICDMAP = computer algorithm; ID = identification, ISS = Injury Severity Score, LOC = loss of consciousness, MN = Minnesota, PAS = Professional Activities Study, PTA = posttraumatic amnesia, TBI = traumatic brain injury, US = United States.

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TABLE 3.3 Non-US Incidence Studies: Case identification, data score, and TBI severity score

Reference	Year(s) of Data	Location	Case Definition and Data Source	TBI Severity Criteria and Scoring
Jennett and MacMillan, 1981	1974	England, Wales and Scotland	Death records, hospital admission records with ICD 800, 801, 803, 804, 850-4	Not reported
Selecki et al., 1981	1977	New South Wales and South Australia	Hospital inpatient statistics of Health Commission ICD-8 for principal diagnosis	Not reported
Servadei et al., 1985	1981 to 1982	San Marino Republic	Medical record review with those with skull fracture or LOC hospital admitted	Evaluated by GCS but not reported
Wang et al, 1986	1983	Urban areas of China	Survey of 6 cities with door-to-door interviews and medical record followup	Survey included only a survival population. Severity not evaluated
Nestvold et al, 1988	1974	Central Norway, Akershus County (Oslo)	Prospective identification by surgeons on duty case inclusion with neurological symptoms	Survey ranked by length of PTA: None = 1,< 0.5 hr = 2, 0.5- 6 hr = 3, 6-24 hr = 4, 1-2 days = 5, 3-7 days = 6, > 7 days = 7
Servadei et al, 1988	1981 to 1982	Ravenna, Italy	ED identification plus hospital admission and record review	GCS; 3-5, 6-8, 9-12, 13-15
Badcock, 1988	1984	South Australia	Prospective study of all ED visits, hospital admissions and prehospital deaths	Length of PTA: none, < 5 min, 5-60 min, 1-24 hrs, 1-7 days, 1-4 wks, > 4 wks
Tiret et al., 1990	1986	Aquitaine, France	Prehospital deaths and hospital admissions survey by medical staff using 180 possible head injury codes using AIS and ISS	Severity by 3 classes based on PTA of coma > 6 hrs = severe, PTA 15 min to 6 hrs = moderate, PTA, 15 min = mild
Levi et al., 1990	1984 to 1988	Northern Israel	Prospective patient identification from referral to neurological service records	GCS used but not recorded
Nell and Brown, 1991	1986	Johannesburg, South Africa	Inpatient admission with screening ICD-9 codes 800-804, 850-854, 293, 294, 310, 870-873, 950-951, 958, 345, 347, 348, 253.9	GCS, mild = 13-15, moderate = 7-12 and severe = 3-6

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Reference	Year(s) of Data	Location	Case Definition and Data Source	TBI Severity Criteria and Scoring
Johansson et al., 1991	1984 to 1985	Northern Sweden	Hospital admissions with ICD 850-854	Severity not evaluated
Annoni et al., 1992	1987	Canton St. Gallen, Switzerland	Hospitalized patients with intracranial lesions on admission CT	Severe brain injury only GCS < 7, 7-9, 10-12, > 12
Vazqueg-Barguero et al., 1992	1988	Cantabria, Spain	Hospital admissions with objective neurological findings such as LOC, skull fracture	GCS, minor = 13-15, moderate 9-12, severe 3-8
Engberg, 1995	1988	Frederiksborg County, Denmark	ED and hospital ICUs in 4 hospitals using hospital records, Danish Hospital Register and National Register	Severity by PTA: 24 hrs-7 days = severe, very severe = > 7 days
Chiu et al., 1997	1988 to 1994	Taiwan	Hospital admission with LOC, skull fracture, neurological deficit or CT intracranial hemorrhage	GCS: mild = 13-5, moderate = 9-12 (or CT pos), severe = < 8
Hillier et al., 1997	1987	South Australia	All public and private hospitals with admission ICD-9 codes of 348, 800, 803, 804, 850-854	GCS: mild = 13-5, moderate = 9-12 (or CT pos), severe = 3- 8; PTA < 30 min = mild, 30-60 min = moderate, > 60 min = severe, PTA < 60 min = mild, 60 min = moderate, 24 hrs = severe
Ingebrigtsen et al., 1998	1993	Northern Norway	All patient referral medical records includes ED visits excludes scalp, facial injuries	GCS: minimal = 15 no LOC, mild = 14 or 15 plus PTA or brief LOC or impaired alertness, moderate = 9-13 or LOC > 5 min or focal neurological deficit, severe = 5-8, critical = 3-4
Tate et al., 1998	1988	New South Wales, Australia	Admission to region hospital with ICD-9 codes 310, 800, 801, 803, 804, 850-854, 905.0, 907	Severe = PTA > 24 hrs, or GCS of < 9, moderate = PTA 1-24 hrs or GCS 9-12, mild = PTA or LOC < 1 hr
Alaranta et al., 2000	1991 to 1995	Finland	Hospital discharge or register using ICD-9 codes: 800, 801, 803, 850-854 (1st time patients only)	Severity not evaluated
Pickett et al., 2001	1988	Greater Kingston Area of Canada	Computerized ED injury records from the CHIRPP system	Severity not reported
Engberg and Teasdale, 2001	1979 to 1996	Denmark	Danish National Hospital Register using 8th ICD codes 800, 801, 803, 850-854, mortality data from National Death Register using ICD 8th and 10th codes	Severity not evaluated

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Reference	Year(s) of Data	Location	Case Definition and Data Source	TBI Severity Criteria and Scoring
Masson et al., 2001	1996	Aquitaine, France	Persons hospital admitted through emergency service with of any one of 19 hospitals, data from treating hospital	AIS score of 4 or 5 or LOC 6-24 hrs GCS < 9
Firchging and Woischneck, 2001	1996	Germany	Head injury hospital admitted patients including concussion; deaths from Federal Bureau of Statistics	Severity scoring not reported
Gururaj, 2002	1999	Bangalore, India	Case definitions from the Neurotrauma Registry of National Institute of Mental Health and Neuroscience, Bangalore India including LOC or PTA neurological changes, skull fracture, death due to TBI	GCS used by categories of severity not defined
Servadei et al., 2002b	1998	Romagna and Trentino, Italy	Hospital admissions with ICD-9 codes 800.0-800.3, 801.0-801.3, 803.0-803.3, 850; 851.0-851.1, 852.0-852.1 853.0-853.1, 854.0-854.1	Severity not evaluated
Servadei et al., 2002a	1998	Romagna, Italy	All patients admitted to hospital care with a discharge diagnosis of ICD-9 800.0-803.0, 801.0-801.3, 803.0-804.3, 850-854. In hospital and prehospital deaths identified from hospital records or death certificates	Mild TBI as defined by Duckin using ICD codes GCS of 14-15 = mild, 9-13 = moderate, < 9 = severe
Masson et al., 2003	1996	Aquitaine, France	Persons admitted to anyone of 19 public hospitals with prolonged coma determined by LOC > 24 hrs or GCS of < 9 before sedation	Severe TBI by GCS of < 9 for at least 24 hrs
Kleiven et al., 2003	1987 to 2000	Sweden	National hospital discharge register using ICD codes 800-804, 850-854, (ICD-9) and S2.0-S2.9, S6.0-S6.9 (ICD-10)	Severity not evaluated
Andersson et al., 2003	1992 to 1993	Western Sweden	Persons identified from hospitals ED unit, discharge register, regional neurological clinic and coroner's records ICD-9, 850-854, 800-804	Mix of symptoms defined by American Congress of Rehabilitation Medicine
Baldo et al., 2003	1966 to 2000	Northeast Italy	Hospital discharges with ICD-9 codes 800.0, 801.9, 803.0, 804.9, 850.0,-854.1 located on data base for region	ICDMAP-90 used to convert ICD codes to AIS: 1/2 = mild, 3 = moderate, 4/5 = severe
Santos et al., 2003	1994, 1996, 1997	Portugal	From National Institute of Statistics using ICD-9 codes 800, 801, 803, 804, 850-854, 907.0 for hospital discharge and mortality data	Severity not evaluated

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Reference	Year(s) of Data	Location	Case Definition and Data Source	TBI Severity Criteria and Scoring
Steudel et al., 2005	1972 to 1998	Germany	Federal Bureau of Statistics using ICD-9 codes 800-804 and 850-854 and ICD-10 S02.0-S02.9 and S06.0-S06.9	Focus of study is on fatal head injury
Tennant, 2005	2001 to 2003	England	Hospital Episodes Statistics using ICD-10 codes S00.0-S09.9 for hospital in-patient care plus Primary Care Trusts	Severity not evaluated
Chiu et al., 2007	1991, 2001	Taipei City and Hualien County, Taiwan	Prospective TBI registry data. Excludes pre-hospital deaths in 2001	GCS: severe = < 9, moderate = 9-15 plus hospital stay at least 48 hrs and had brain surgery or abnormal CT scan, mild = all others
Yates et al., 2008	1997 to 2003	Royal Devon and Exeter Hospital, UK	ED database from one hospital. ICD codes used but not stated	Based on ICD-10 but not defined
Wu et al., 2008	2004	6 Providences of Eastern China	Hospital admitted patients with data from attending physician	GCS: severe = < 9, moderate = 9-13, mild = 14, 15

NOTE: AIS = Abbreviated Injury Scale, CHIRPP = Canadian Hospitals Injury Reporting and Prevention Program, CT = computed tomography, ED = emergency department, GCS = Glasgow Coma Scale, ICD = International Classification of Diseases, ICDMAP = computer algorithm, ICU = intensive care unit, ISS = Injury Severity Score, LOC = loss of consciousness, PTA = posttraumatic amnesia, TBI = traumatic brain injury, UK = United Kingdom.

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TABLE 3.4 US TBI Incidence Studies

Reference	Year(s) of Data	Location	Number of Patients	Base Population (x1000)	Rate / 10^5 per year	Comments
Annegers et al., 1980	1965 to 1974	Olmstead County, MN	3587	NS	193	Age adjusted to 1970 US population, rate averaged from men only and women only rates
Fuortes et al., 1990	1984 to 1986	Iowa	NS	NS	159 in 1984 133 in 1985 117 in 1986	Hospital admissions only
Rimel, 1981	1977 to 1979	Central Virginia	1330	NS	NS	Hospital patients and prehospital deaths
Klauber et al., 1981	1978	San Diego, CA	5055	NS	294	Includes some nonresidents, excludes a few external causes
Cooper et al., 1983	1980 to 1981	Bronx, NY	1209	NS	249	Rate based on sample, age adjusted to 1980 US population
Jagger et al., 1984b	1978	North Central Virginia	735	354	208	Rate includes residents and nonresidents; no ED cases or prehospital deaths
Kraus et al., 1984	1981	San Diego County, CA	3358	1862	180	Population based, not age adjusted
Whitman et al., 1984	1979 to 1980	Inner city Chicago and Evanston, IL	782	213	331	Composite rate from data in publication, average across race and gender
Fife et al., 1986	1979 to 1980	Rhode Island	2870	947	152	Hospital patients only
Fife, 1987	1977 to 1981	US	307,000 1.87 million	226,545 1.87 million	136 805	Hospital patients only; All injured patients
MacKenzie et al., 1989a	1986	Maryland	5838	NS	132	Hospital patients only
MacKenzie et al., 1990	1979 to 1986	Maryland	NS	NS	114-134	Hospital patients only, range in rates
Oklahoma State Department of Health, 1991	1989	Oklahoma	3672	NS	121	Hospital and fatal cases
Schuster, 1994	1990	Massachusetts	27,819	6016	10 86 366	Mortality rate Hospital admissions ED only
Warren et al., 1995	1991 to 1993	Alaska	2178	457	130	Hospital patients only
Diamond, 1996	1988 to 1993	Virginia	46,680	NS	NS	Only age specific rates reported
Sosin et al., 1996	1991	US	1.54 million	NS	618 158	Total rate Hospitalized

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Reference	Year(s) of Data	Location	Number of Patients	Base Population (x1000)	Rate / 10^5 per year	Comments
					307 153	ED only No care
Thurman et al., 1996	1990 to 1992	Utah	5782	NS	106	Age adjusted rate to 1990 US population
Gabella et al., 1997a	1990 to 1993	Colorado, Missouri, Oklahoma, Utah	13,978	13,687	103	Age adjusted rate to 1990 US population
Gabella et al., 1997b	1991 to 1992	Colorado	7056	NS	101	Hospitalized and deaths, age adjusted to US
Thurman and Guerrero, 1999	1994 to 1995	US	NS	NS	98	Hospitalized patients only
Jager et al., 2000	1992 to 1994	US	1.144 million	NS	444	ED patients only
Schootman et al., 2000	1993	Iowa	2559	NS	91	Severe TBI rate based capture-recapture; age adjusted rate to 1990 US population
Guerrero et al., 2000	1995 to 1996	US	1.027 million	NS	392	ED patients only
Louisiana Office of Public Health Injury and Research Prevention Section, 2004	1996 to 1999	Louisiana	16,203	NS	90	Hospitalized patients and prehospital deaths
Langlois et al., 2003	1997	14 US states	62,771	NS	70	Live hospital discharges only
Langlois et al., 2006	1995 to 2001	US	1.396 million	NS	505	Total rate, Age adjusted to 2000 US population
			235 1.111 million		86 401	Hospitalized patients only ED visits only
Selassie et al., 2004	1996 to 2001	South Carolina	70,671	NS	68 220	Hospital patients only ED patients only
Texas Department of Health, 2004	1998	Texas	20,000	NS	NS	Hospitalized patients only
Rutland-Brown et al., 2006	2003	US	1.565 million	NS	538 421 100	Total ED visits only Hospitalization

NOTE: CA = California, ED = emergency department, IL = Illinois, MN = Minnesota, NS = not stated, NY = New York, TBI = traumatic brain injury, US = United States.

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TABLE 3.5 Non-US TBI Incidence Data

Reference	Year(s) of Data	Location	Number of Patients	Base Population (x1000)	Rate / 10^5 per year	Comments
Jennett and MacMillan, 1981	1974	England, Wales and Scotland	NS	NS	270 in England and Wales 313 in Scotland	Annual rates based on sample weeks, rates not age adjusted
Selecki et al., 1981	1977	New South Wales, Australia	18,678	4960	377	Hospital admissions only excludes prehospitalized deaths
Servadei et al., 1985	1981 to 1982	San Marino	327	23.5	468	Hospital admissions
Wang et al., 1986	1982	Urban areas of China	35	63	56	Rates based on samples of households in city communities
Nestvold et al., 1988	1974	Central Norway	488	350	236	Hospital admissions
Badcock, 1988	1984	South Australia	1698	NS	520	Includes ED visits, admissions and prehospital deaths
Servadei et al., 1988	1984	Ravenna, Italy	644	172	372	Hospitalized cases only excludes ED treated and released
Levi et al., 1990	1984 to1988	Northern Israel	1370	1200	25	Rate in person–years
Tiret et al., 1990	1986	Aquitaine, France	8940	2700	281	Hospital admissions and deaths
Johansson et al., 1991	1984 to 1985	Northern Sweden	242	70	242	Ages 16-60 only, hospital admissions
Nell and Brown, 1991	1986	Johannesburg, South Africa	5106	NS	316	Rate based on population estimates
Annoni et al., 1992	1987	St. Gallon Canton of Switzerland	80	410	20	Rate based on sample of hospital weeks of data collection
Vazquez-Barquero et al., 1992	1988	Cantabria, Spain	477	523	91	Hospital admissions only
Engberg, 1995	1988	Frederiksborg County, Denmark	NS	340	22.6 (7.1)	ICD 851-4 only (PTA $\geq$ 7 days)
Chiu et al., 1997	1988 to 1994	Taiwan	58,563	NS	Taipei: 220 Hualien Co: 30	Number of patients excludes prehospital deaths; rates include nonhospital deaths
Hillier et al., 1997	1987	South Australia	4486	1393	322	Rate for persons 16+, excludes prehospital deaths

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Reference	Year(s) of Data	Location	Number of Patients	Base Population (x1000)	Rate / 10^5 per year	Comments
Ingebrigtsen et al., 1998	1993	Northern Norway	247	108	229	Hospital referred patients
Tate et al., 1998	1988	New South Wales	1259	NS	100	Hospital admitted patients excludes prehospital deaths
Alaranta et al., 2000	1991 to 1995	Finland	24,497	5100	95-100	Hospital discharge first-time TBI patients only, rate range over 5 years
Engberg and Teasdale, 2001	1979 to 1996	Denmark	NS	NS	265 224 157	Hospitalized patients trend from 1979-1981, 1985-1987, 1991-1993, excludes prehospital deaths
Firsching and Woischneck, 2001	1996	Germany	279,000	82,000	350	Hospital admitted patients only
Masson et al., 2001	1996	Aquitaine, France	497	2800	17.3 (AIS4 = 7.2 AIS5 =10.1)	Total AIS 4 and 5, Severe TBI
Pickett et al., 2001	1998	Kingston, Canada	760	176	431 (115)	Rate calculated from published data (potential head injuries)
Gururaj, 2002	1999	Bangalore, India	NS	NS	160	Hospital admitted patients only
Servadei et al., 2002b	1998	Romagna and Trentino, Italy	3554 (2421, 1133)	1439 (969, 470)	314 (297, 332)	Total for residence, (Romagna, Trentino) hospitalization rates
Servadei et al., 2002a	1998	Romagna, Italy	2430	971	250	Hospital admitted patients only
Andersson et al., 2003	1992 to 1993	Western Sweden	753	138	546	Include ED, hospital admitted and coroner records
Baldo et al., 2003	1996 to 2000	Northeast Italy	55,368	NS	301-212	Hospital admissions 1996-2000
Kleiven et al., 2003	1987 to 2000	Sweden	22,000 per yr	8400-8900	259	Average over 14 years hospital discharged patients
Masson et al., 2003	1996	Aquitaine, France	248	2800	8.5	Coma patients only
Santos et al., 2003	1994, 1996, 1997	Portugal	40,633	9500	151 (1994), 137 (1996, 1997)	All hospital discharges for 1994-1997, plus TBI deaths
Steudel et al., 2005	1998	Germany	276,584	82,000	337	Hospitalized cases and incidence rate; ICD 9 codes 800–804; 850–854
Tennant, 2005	2001 to 2002	England	112,718	NS	229	Hospitalized incidence rate

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Reference	Year(s) of Data	Location	Number of Patients	Base Population (x1000)	Rate / 10^5 per year	Comments
Chiu et al., 2007	2001	Taipei and Hualien County, Taiwan	5754 1474	2634 353	218 417	Excludes prehospital deaths
Wu et al., 2008	2004	6 Provinces of Eastern China	14,948	NS	NS	Hospital admitted cases
Yates et al., 2006	1997 to 2003	England	NS	345	453	From an ED database including hospital admitted

NOTE: AIS = Abbreviated Injury Scale, Co = county, ED = emergency department, ICD = International Classification of Diseases, PTA = posttraumatic amnesia, TBI = traumatic brain injury.

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TABLE 3.6 US TBI Deaths and Mortality Rates

Reference	Year(s) of Data	Location	Number of Deaths	Rate / 10^5 per year	Comments
Annegers et al., 1980	1965 to 1974	Olmsted County, Minnesota	446	Male: 32 Female: 9	Average rates per year
Klauber et al., 1981	1978	San Diego County, California	381	22	Excludes gunshot deaths
Cooper et al., 1983	1980 to 1981	Bronx, New York	NS	28	50% from violence, 75% before hospital admission
Kraus et al., 1984	1981	San Diego County, California	562	30	Includes inhospital and prehospital deaths
Whitman et al., 1984	1979 to 1980	Inner city Chicago and Evanston, IL	54	19 Evanston blacks 11 Evanston whites 32 Inner city	Average rates per year
Fife et al., 1986	1979 to 1980	Rhode Island	248	26/year	Rate derived from data in text
Cowan et al., 1990	1990	Delaware	122	18	59% from motor vehicle crashes
Sosin et al., 1996	1979 to 1986	US	39,416 per yr	17	Death certificate review, average over 8 yrs
Sosin et al., 1996	1979 to 1992	US	52,000	25 in 1979 19 in 1992	Average number of deaths per yr
Thurman et al., 1996	1990 to 1992	Utah	1067	20	Average rate per yr
Gabella et al., 1997b	1991 to 1992	Colorado	1312	18 in urban regions 34 in rural regions	
Gabella et al., 1997a	1990 to 1992	Colorado, Missouri, Oklahoma, Utah	3172	23	Average rate per yr
Thurman et al., 1999	1994	US	51,350	20	Data source is state TBI registry
Adekoya et al., 2002	1989 to 1998	US	53,288 per yr	21	22 in 1989 19 in 1998
Langlois et al., 2006	1995 to 2001	US	49,900 per yr	18	Average rate over 7 years
Rutland-Brown et al., 2006	2003	US	51,000	18	

NOTE: IL = Illinois, US = United States, TBI = traumatic brain injury.

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TABLE 3.7 Non-US TBI Deaths and Mortality Rates

Reference	Year(s) of Data	Location	Number of Deaths	Rate / 10^5 per year	Comments
Jennett and MacMillan, 1981	1972 to 1976	England, Wales and Scotland	NS	9	Average over 5 years
Simpson et al., 1981	1977	New South Wales and South Australia	1727	28	Average for both regions
Badcock, 1988	1984	South Australia	NS	6	
Nestvold et al., 1988	1974	Central Norway	23	7[a]	Prehospital plus inhospital deaths
Servadei et al., 1988	1984	Ravenna, Italy	42	24	Source of mortality data not given
Levi et al., 1990	1984 to 1988	Northern Israel	59[b]	3	Source of mortality not given
Tiret et al., 1990	1986	Aquitaine, France	391	22	Source was mortality statistics for Aquitaine
Johansson et al., 1991	1984–1985	Northern Sweden	14	12	For ages 16-60 years only
Nell and Brown, 1991	1986	Johannesburg, South Africa	1303	80	Source is coronal file. Rate over 190/100,000 for blacks age 25-44
Vazquez-Barquero et al., 1992	1988	Cantabria, Spain	103	20	Death rates higher for males
Engberg, 1995	1988	Frederiksborg County, Denmark	45	13	Computerized search of death records
Chiu et al., 1997	1988 to 1994	Taipei, Hualien County, Taiwan	2621	20 82	
Engberg and Teasdale, 2001	1979 to 1996	Denmark	NS	11	1994 to 1996 average
Firsching and Woischneck, 2001	1996	Germany	9415	12	
Masson et al., 2001	1996	Aquitaine, France	149	5	Limited to severe TBI only
Gururaj, 2002	1999	Bangalore, India	NS	20	
Servadei et al., 2002b	1998	Romagna and Trentino, Italy	85 (75, 10)	5 (8, 2)	In hospital deaths
Servadei et al., 2002a	1998	Romagna, Italy	225	18	Highest rates for 5-24 and 75+
Andersson et al., 2003	1992 to 1993	Western Sweden	5	4	Few coma patients
Baldo et al., 2003	1996 to 2000	Northeast Italy	NS	7	Average rate over 4 years
Masson et al., 2003	1996	Aquitaine, France	128	5	Coma patients only, rate derived from text
Santos et al., 2003	1994, 1996, 1997	Portugal	5425	17	Highest rate for those age 20-29, 80+

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Reference	Year(s) of Data	Location	Number of Deaths	Rate / 10^5 per year	Comments
Steudel et al., 2005	2000	Germany	7567	9	Represents 67% decrease from 1972

[a] = rate derived from data in narrative
[b] = includes work and other
NOTE: NS = not stated, TBI = traumatic brain injury.

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TABLE 3.8 Percent Severity Distributions of Hospitalized Patients in US and Non-US Incidence Studies

Reference	Year(s) of Data	Location	Percent Mild	Percent Moderate	Percent Severe	Comments
Annegers et al., 1980	1965 to 1974	Olmsted County, MN	63	29	7	See table 3 for criteria
Rimel, 1981	1977 to 1979	Central Virginia	49	26	25	Based on GCS
Klauber et al., 1981	1978	San Diego County, California		91	25	91% includes mild and moderate. Mild = 12-15
Whitman et al., 1984	1979 to 1980	Innercity Chicago and Evanston, IL	86	9	5	Severity criteria same as Annegers, see table 3
Kraus et al., 1984	1981	San Diego County, California	82	9	9	Using slightly modified GCS
Badcock, 1988	1984	South Australia	90	8	2	Based on PTA
Tiret et al., 1990	1986	Aquitaine, France	80	11	9	Based on LOC and AIS
Nell and Brown, 1991	1986	Johannesburg	87	8	5	GCS moderate = 7-12, severe = 3-6
Vazquey- Barguero et al., 1992	1988	Cantabria, Spain	88	7	5	Based on GCS
Thurman et al., 1996	1990 to 1992	Utah	39	42	19	Using the GCS
Chiu et al., 1997	1988 to 1994	Taiwan	79	9	12	Based on GCS over 7 years
Hillier et al., 1997	1987	South Australia	75 82 82	9 3 9	16 15 9	Based on GCS, ICDMAP, PTA, respectively
Tate et al., 1998	1988	New South Wales	65	21	14	Based on PTA
Thurman et al., 1999	1980 to 1995	US	78	16 23	6	1980-1981 (Used ICDMAP to create AIS 1994-1995)
Gururaj, 2002	1999	Bangalore, India	70	14	16	Based on GCS
Servadei et al., 2002a	1998	Romagna, Italy	66	7	27	Mild = 14-15, Moderate = 9-13
Baldo et al., 2003	1991 to 2000	Northeast Italy	69 63	22 16	9 21	1996 2000; Used GCS
Chiu et al., 2007	1991 vs. 2001	Taipei and Hualien County, Taiwan	78 77 87 83	10 9 6 9	12 14 7 8	Taipei 1991 Taipei 2001 Hualien County 1991 Hualien County 2001 Based on GCS

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Reference	Year(s) of Data	Location	Percent Mild	Percent Moderate	Percent Severe	Comments
Wu et al., 2008	2004	6 Provinces of Eastern China	62	18	20	Used GCS

NOTE: AIS = Abbreviated Injury Scale, GCS = Glasgow Coma Scale, ICDMAP = computer algorithm, IL = Illinois, LOC = loss of consciousness, MN = Minnesota, PTA = posttraumatic amnesia.

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TABLE 3.9 Highest Age-Specific TBI Rates and Gender Rate Ratios: US Studies

References	Highest Age Ranges	Male / Female Rate Ratio
Annegers et al., 1980	15 – 24	2.3
Klauber et al., 1981	15 – 19, 20 – 29, 70+	1.3 - 1.8
Cooper et al., 1983	20 – 39	2.8
Jagger et al., 1984b	15 – 19, 20 – 24, 25 – 29	2.4
Whitman et al., 1984	Varied by race/community	2.5
Kraus et al., 1984	15 – 24, 70+	2.2
Fife et al., 1986	15 – 25, < 10, 75+	2
MacKenzie et al., 1989a	15 – 24, 75+	2.1
MacKenzie et al., 1990	15 – 24, 75+	2.1
Fuortes et al., 1990	15 – 19	NS
Oklahoma State Department of Health, 1991	15 – 19, 20 – 24, 60+	2
Schuster, 1994	15 – 24, 0 – 4	1.5
Warren et al., 1995	85+, 15 – 24	2.4
Thurman et al., 1996	≥ 75, 15 – 24	2.1
Diamond, 1996	0 – 5, 11 – 19, 20 – 29	1.4
Sosin et al., 1996	15 – 24	1.6[a]
Gabella et al., 1997b	15 – 24, 65+	2
Gabella et al., 1997a	15 – 24, 75+	2.1
Thurman and Guerrero, 1999	1980 to 1981 = 15 – 24, 0 – 4 1994 to 1995 = 65+, 15 – 24	2
Jager et al., 2000	0 – 4, 85+, 15 – 24	1.7
Guerrero et al., 2000	0 – 14, 15 – 24	1.6[b]
Schootman et al., 2000	15 – 24, 75 – 84	1.9
Louisiana Office of Public Health Injury and Research Prevention Section, 2004	85+, 75 – 84, 15 – 24	2
Langlois et al., 2003	65+, 15 – 19	1.9
Langlois et al., 2006	0 – 4, 15 – 19, 75+	1.5
Texas Department of Health, 2004	20 – 24, 75+	2.1
Rutland-Brown et al., 2006	0 – 4, 5 – 24	1.5

[a] = mild and moderate only
[b] = ED patients only
NOTE: ED = emergency department, NS = not stated.

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TABLE 3.10 Highest Age-Specific TBI Rates and Gender Rate Ratios: Non-US Studies

Reference	Highest Age Ranges	Male / Female Rate Ratio
Jennett and MacMillan, 1981	15-19, 0-4	NS
Wang et al., 1986	40-49	1.6
Nestvold et al., 1988	10-19, 20-29	1.9
Servadei et al., 1988	NS	1.6
Badcock, 1988	15-19, 0-4	2
Levi et al., 1990	0-4, 75+	2.7
Tiret et al., 1990	< 5, 15-24, 75+	2.1
Johansson et al., 1991	15-24	3.2[a]
Nell and Brown, 1991	Africans: 25-44, 15-24 Whites: 15-24, 65+	4.6 9.3
Annoni et al., 1992	NS	3.1
Vazquez-Barquero et al., 1992	15-25, < 15	2.9
Engberg, 1995	65+	2.1
Chiu et al., 1997	20-29, 10-19, 30-39	2.2
Hillier et al., 1997	16-25	2.3[b]
Ingebrigtsen et al., 1998	0-9, 10-24, 85+	1.7
Tate et al., 1998	15-24	2.7[c]
Alaranta et al., 2000	Males: 0-9 Females: 70+	1.5
Engberg and Teasdale, 2001	Varied by ICD diagnosis	NS
Masson et al., 2001	75+, 15-29	2.5[d]
Pickett et al., 2001	10-19, < 9	1.7
Servadei et al., 2002a	1-4, 15-24, 75+	1.6
Andersson et al., 2003	0-9, 10-19	1.5
Baldo et al., 2003	NS	1.6
Kleiven et al., 2003	Males: 15-19, 85+ Females: 0-4, 85+	2.1
Masson et al., 2003	75+	3.1[e]
Santos et al., 2003	20-29, 80+	1.8[c]
Steudel et al., 2005	75-90	NS
Chiu et al., 2007	20-29 (2001), 70+ (1991)	2.1
Yates et al., 2006	15-19, 80-84, 0-5	NS

[a] = ages 16-60
[b] = ages 16+
[c] = cases, not rates
[d] = severe brain injury
[e] = patients in coma
NOTE: NS = not stated, TBI = traumatic brain injury.

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TABLE 3.11 Percent Distributions of TBI Incidence Cases by External Cause: US Studies

Reference	Transport	Falls	Firearms / Violence[a]	Sport / Recreation	Other[b]
Annegers et al., 1980	40	29	6	16	8
Klauber et al., 1981	53	NS	NS	6	41
Rimel, 1981	55	18	12	17	NS
Cooper et al., 1983	27	32	34	NS	NS
Jagger et al., 1984b	55	20	11	NS	14
Kraus et al., 1984	48	21	18	10	4
Whitman et al., 1984	32	21	35	5	6
Fife et al., 1986	39	35	9	NS	17
MacKenzie et al., 1989a	49	26	11	NS	14
Oklahoma State Department of Health, 1991	42	25	19	8	6
Cowan et al., 1990[f]	59	3	37	NS	2
Schuster, 1994	33	30	18	NS	20
Warren et al., 1995	31	20	21	20	7
Thurman et al., 1996	54	21	15	6	4
Sosin et al., 1996[c]	28	NS	9	20	43
Jager et al., 2000[d]	29	39	NS	NS	32
Gabella et al., 1997a	48	23	18	3	9
Guerrero et al., 2000[d]	22	31	35	NS	11
Adekoya et al., 2002[f]	34	10	40	NS	16
Louisiana Office of Public Health Injury and Research Prevention Section, 2004	46	34	12	NS	8
Langlois et al., 2006[e]	39	28	11	NS	22
Texas Department of Health, 2004	48	20	12	NS	20
Rutland-Brown et al., 2006	19	32	10	NS	39

[a] = includes self-inflicted
[b] = includes work and other
[c] = mild and moderate
[d] = ED visits only
[e] = hospital admits only
[f] = mortality data
NOTE: NS = not stated, TBI = traumatic brain injury.

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TABLE 3.12 Percent Distributions of TBI Incidence Cases by External Cause: Non-US Studies

Reference	Transport	Falls	Firearms / Violence[a]	Sport / Recreation	Other[b]
Tiret et al., 1990	60	33	<1	NS	7
Nell and Brown, 1991[c]	Females: 40	3	39	NS	16
	Males: 36	4	46		15
Vazquez-Barquero et al., 1992	60	24	NS	NS	16
Chiu et al., 1997	69	20	7	1	3
Hillier et al., 1997	57	29	10	NS	4
Servadei et al., 1988	69	26	1	NS	5
Ingebrigtsen et al., 1998	21	62	7	NS	10
Tate et al., 1998	40	20	8	25	6
Alaranta et al., 2000	26	61	5	NS	8
Firsching and Woischneck, 2001	56	31	12	NS	NS
Masson et al., 2001	48	42	3	NS	7
Servadei et al., 2002a	48	33	1	1	17
Andersson et al., 2003	16	58	NS	NS	26
Kleiven et al., 2003	26	54	15	NS	7
Masson et al., 2003	59	16	10	NS	14
Chiu et al., 2007	Taipei: 45	34	11	NS	10
	Hualien Co:55	28	13	NS	4

[a] includes self-inflicted injury,
[b] includes work and all other causes,
[c] both races, nonfatal TBI
NOTE: Co = county, NS=not stated.

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TABLE 3.13 TBI in-Hospital Case Fatality Rates (CFR) from US Population Based Studies

Reference	Location	Source of Data and Study Population	N = Sample Size	CFR %
Rimel, 1981	Central Virginia	Hospital medical records	N = 1330	7.0
Cooper et al., 1983	Bronx, New York	Hospital medical and medical exam records	N = 1209	24.9
Kraus et al., 1984	San Diego County, California	Hospital medical records and medical exam records	N = 3358	5.2
Whitman et al., 1984	Chicago area	Hospital medical records and medical exam records	N = 782	6.9
Jagger, 1984b	North Central Virginia	Hospital records	N = 735	6.5
Fife et al., 1986	Rhode Island	Hospital records	N = 2870	4.9
MacKenzie et al., 1989a	Maryland	Hospital records	N = 5838	4.4
Oklahoma State Department of Health, 1991	Oklahoma	Hospital/medical examiner records	N = 3672	23
Schuster, 1994	Massachusetts	Hospital/medical examiner records	N = 5778	10.1
Warren et al., 1995	Alaska	Trauma registry	N = 2178	5.6
Gabella et al., 1997b	Colorado	TBI surveillance	N = 6863	7.6
Gabella et al., 1997a	Colorado, Missouri, Oklahoma, Utah	Hospital discharge data	N = 11,611	6.9
Langlois et al., 2003	US	14 state TBI surveillance system	N = 67,309	6.9
Rutland-Brown et al., 2006	US	National Hospital Discharge Survey and Multiple Cause of Death tape	N = 340,757	14.9
Langlois et al., 2006	US	Same as Rutland-Brown, 2003	N = 284,900	17.5

NOTE: CFR = case fatality rate, TBI = traumatic brain injury.

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TABLE 3.14 TBI in-Hospital Case Fatality Rates (CFR) from Non-US Population Based Studies

Reference	Location	Source of Data and Study Population	Group Size	CFR %
Badcock, 1988	South Australia	Medical record	1698	0.8
Nestvold et al., 1988	Norway	Medical record	488	3.3[a]
Servadei et al., 1988	Ravenna, Italy	Hospital record	578	1.9[a]
Tiret et al., 1990	Aquitaine, France	Medical record review	281	4.4
Vazquez-Barquero et al., 1992	Cantabria, Spain	Hospital record review	477	1.7
Engberg, 1995	Frederisksborg County, Denmark	National hospital discharge registry	95	16[a]
Tate et al., 1998	New South Wales	Hospital record review	1259	3.9
Engberg and Teasdale, 2001	Denmark	National hospital discharge registry	NS	30[b]
Gururaj, 2002	Bangalore, India	Neurotrauma registry	2814	9
Servadei et al., 2002b	Romagna and Trentino, Italy	Hospital discharge records	4442	1.0[a]
Servadei et al., 2002a	Romagna, Italy	Hospital discharge records	2430	2.8[d]
Baldo et al., 2003	Northeast Italy	Hospital discharge records	11,074	3.2[c]
Santos et al., 2003	Portugal	National Institute of Statistics	39,042	9.8[a]
Steudel et al., 2005	Germany	Federal Bureau of Statistics	276,758	1
Chiu et al., 2007	Taipei and Hualien County, Taiwan	TBI registry	Taipei: 5754 Hualein County: 1474	Taipei: 5.4 Hualein County: 6.7

a = CFR derived from text
b = CFR for ICD 851-854
c = from severity rates reported
d = for residents and nonresidents
NOTE: CFR = case fatality rates, TBI = traumatic brain injury.

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TABLE 3.15 Percent Distribution of GOS Outcome Categories at Hospital Discharge Rate for US and Non-US Studies

Reference	Good Recovery	Moderate Disability	Severe Disability	Persistent Vegetative State	Death
Rimel, 1981	69	12	8	4	7
Kraus et al., 1984	90	3	1	0.5	6
Chiu et al., 1997	87	4	3	1	5
Masson et al., 2003	18	9	16	3	52
Langlois et al., 2003	74	10	6	0.6	NS
Chiu et al., 1997 (Taipei City only)	87	6	4	0.3	3
Wu et al., 2008	77	7	2	3	11

NOTE: GOS = Glasgow Outcome Score, NS = not stated

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4

CONSIDERATIONS IN IDENTIFYING AND EVALUATING THE LITERATURE

This chapter presents the approach that the committee used to identify and evaluate the literature on traumatic brain injury (TBI). It provides information regarding how the committee searched the literature and discusses the major types of studies considered. The chapter also includes a discussion of the committee's evaluation criteria, the limitations of the studies reviewed, and the categories of association that the committee used in drawing conclusions about association.

As noted in Chapter 1, the committee was charged with drawing conclusions about the association between TBI and subsequent long-term health outcomes. The legislation originally establishing this type of review (PL 105-277 and PL 105-368) does not direct the committee to look at specific diseases or outcomes but rather to look broadly for health effects that might be associated with the exposure under study. In this instance, the exposure of interest is a TBI. The committee's literature searches led to the numerous health outcomes that are discussed in the report.

Thus, the committee sought to characterize and weigh the strengths and limitations of the available evidence as presented in the studies it reviewed. The committee did not concern itself with policy issues, such as potential costs of compensation, policies regarding compensation, or any broader policy implications of its findings.

IDENTIFICATION OF THE LITERATURE

The committee began its work by overseeing extensive searches of the peer-reviewed medical and scientific literature, including published articles, other peer-reviewed reports, and dissertations. The searches retrieved over 30,000 potentially useful epidemiologic studies, and the titles and abstracts of those studies were reviewed. The committee focused its attention on clinical and epidemiologic studies of adults with long-term health effects that resulted from a TBI by any mechanism, such as occupational injury, motor-vehicle collision, sports injury, gunshot wound, or other act of violence, including military combat injury. Studies of patients with a TBI due to malignancy, stroke, infection, ischemia, other diseases or disorders of the brain, intoxication, or oxygen deprivation were not considered. The committee did not systematically review studies of young children, the elderly, or brain-injured patients in litigation for compensation claims. The review excluded case reports, case series with few participants,

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and studies of acute outcomes that resolved within days to a few months. The committee did not review general studies of "disability" as a gross measure of morbidity but rather evaluated studies that associated TBI with specific health outcomes.

After its assessment of the 30,000 titles and abstracts, the committee members identified about 1,900 studies for further review. Those studies were objectively evaluated without preconceived ideas about health outcomes or the existence or absence of associations. To assist them in their evaluation, the committee members developed inclusion criteria (see below) to determine which of the 1,900 studies would be included in its review.

The committee adopted a policy of using only peer-reviewed published literature or unpublished reports that had undergone rigorous peer review, such as dissertations and some government reports, as the basis of its conclusions. The process of peer review by fellow professionals increases the likelihood of high quality but does not guarantee the validity of a study or the ability to generalize its findings. Accordingly, committee members read each study critically and considered its relevance and quality. They did not collect original data, nor did they perform any secondary data analysis.

In light of that orientation to the committee's task and approach, the following section briefly discusses types of evidence and the value of epidemiologic or clinical studies in determining whether an association exists. It is followed by a discussion of the committee's specific inclusion criteria that were developed to help in deciding whether a study would be included and evaluated. The committee also notes the numerous factors that it considered in evaluating the evidence in a study and, finally, presents the categories of association used in drawing conclusions about the strength of associations.

TYPES OF EVIDENCE

The committee relied entirely on clinical and epidemiologic studies to draw its conclusions about the strength of evidence of associations between TBI and health effects. However, animal studies play a critical role in clarifying the mechanism of TBI (see Chapter 2) and in providing biologic understanding of many of the effects seen in humans.

Animal Studies

Studies of laboratory animals are essential for understanding mechanisms of action and biologic plausibility and for providing information about possible health effects when experimental research in humans is not ethically or practically possible (NRC, 1991). Such studies permit an injury caused by a blast or other mechanism to be introduced under conditions controlled by the researcher. Mechanism-of-action (mechanistic) studies encompass a variety of laboratory approaches with whole animals and in vitro systems that use tissues or cells from humans or animals.

In deciding on associations between TBI and human health effects, the committee used evidence only from human studies, in some cases, however, it examined animal studies as a basis of judgments about biologic mechanism or plausibility.

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Epidemiologic Studies

Analytic epidemiologic studies examine the association between two or more variables. *Predictor variable* and *independent variable* are terms for an exposure to an agent of interest in a human population. *Outcome variable* and *dependent variable* are terms for a health event seen in that population. Outcomes can also include a number of nonhealth results, such as use of services, social changes, and employment changes. A principal objective of epidemiology is to understand whether exposure to a specific agent is associated with disease occurrence or other health outcomes. That is most straightforwardly accomplished in experimental studies in which the investigator controls the exposure and the association between exposure and outcome can be measured directly. In the case of TBI followup studies, however, human experiments that directly examine the association between TBI and health outcomes are neither ethically nor practically feasible; instead, the association has to be measured in observational studies, and causality has to be inferred. Although they are commonly used synonymously by the general public, the terms *association* and *causation* have distinct meanings (Alpert and Goldberg, 2007).

Associations in Epidemiologic Studies

There are several possible reasons for associations in observational studies: random error (chance); systematic error (bias); confounding; effect–cause; and cause–effect. Spurious associations, that is, the finding of an association that does not truly exist, can be due to random error or chance, systematic error or bias, or a combination of them. Random error or chance is a statistical variation in a measurement taken from a sample of a population that can lead to the appearance of an association when none is present or the failure to find an association when one is present. Systematic error or bias is the result of errors in how the study was designed or conducted. Systematic error can cause an observed value to deviate from its true value and can falsely strengthen or weaken an association or generate a spurious association. Selection bias occurs when there has been systematic error in recruiting a study population, which is different from the target population of the study, with the result that the findings cannot be generalized to the target population. Information bias results from a flaw in how data on exposure or outcome factors are collected.

Other reasons for finding associations that are incorrect are confounding and effect–cause relationships. Confounding occurs when a third variable, termed a confounding variable (or confounder), is associated with both the exposure and the outcome and mistakenly leads to the conclusion that the exposure is associated with the outcome. Effect–cause relationships occur when the outcome precedes the exposure; for example, a study might suggest that a particular psychiatric outcome was associated with a TBI when the psychiatric condition actually preceded the TBI and increased the risk of a TBI. In a true association, the exposure precedes the outcome and the association is free of random error, bias, and confounding (or the chance of them has been minimized); finding these types of associations is the goal of epidemiologic studies.

In epidemiologic studies, the strength of an association between exposure and outcome is generally estimated by using prevalence ratios, relative risks (RRs), odds ratios (ORs), correlation coefficients or hazard ratios (HRs) depending on the type of epidemiologic study performed.To conclude that an association exists, it is necessary for the exposure to be followed by the outcome more (or less in the case of a protective exposure) frequently than it would be expected to by chance alone. The strength of an association is typically expressed as a ratio of

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the frequency of an outcome in a group of participants who have a particular exposure to the frequency in a group without the exposure. A ratio greater than 1.0 indicates that the outcome variable has occurred more frequently in the exposed group, and a ratio less than 1.0 indicates that it has occurred less frequently. Ratios are typically reported with confidence intervals to assess random error. If a confidence interval (95% CI) for a ratio measure (e.g., a relative risk or an odds ratio) includes 1.0, an association is said to be not statistically significant. If the interval does not include 1.0, the association is said to be statistically significant.

Inferring Causality

Determining whether a given statistical association rises to the level of causation requires inference (Hill, 1965); that is, causality is inferred, rather than measured directly, in observational studies. In 1965, Austin Bradford Hill, a British statistician, suggested nine criteria that could be used to assess whether an association observed in an observational study might be causal (Hill, 1965):

- *Strength of association.* A strong association is more likely to have a causal component than a modest association.
- *Consistency*. An association that is observed consistently in different studies is more likely to be causal than one that is not.
- *Specificity*. A factor [or predictor variable] influences specifically a particular outcome or population.
- *Temporality*. A factor must precede an outcome that it is supposed to affect.
- *Biologic gradient (also called dose–response relationship).* An outcome increases monotonically with increasing dose of exposure or according to a function predicted by a substantive theory.
- *Plausibility*. An observed association can be plausibly explained by substantive (for example, biologic) explanations.
- *Coherence.* A causal conclusion should not fundamentally contradict present substantive knowledge.
- *Experiment.* Causation is more likely if evidence is based on randomized experiments.
- *Analogy*. An effect has already been shown for analogous exposures and outcomes.

Some of those criteria, such as experiment and specificity, are not particularly applicable to TBI, but the remaining ones are important for determining causality. A strong association as measured by a high (or low) risk or ratio, an association that is found in a number of studies, an increased risk of disease with increasing exposure or a decline in risk after cessation of exposure, and a finding of the same outcome after analogous exposures (such as sports injuries) all strengthen the likelihood that an association seen in epidemiologic studies is causal. Exposures are rarely, if ever, controlled in observational studies, and with TBI there can be substantial uncertainty in the assessment of exposure. To assess whether explanations other than causality (such as chance, bias, or confounding) are responsible for an observed association, one must bring together evidence from different studies and apply well-established criteria (Hill, 1965; Evans, 1976; Susser, 1973, 1977, 1988, 1991; Wegman et al., 1997). For a recent review of those criteria, see the 2004 report of the US Surgeon General (Office of the Surgeon General-HHS, 2004). A brief discussion of the more important ones follows.

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Strength of Association

The strength of an association is usually expressed as the magnitude of the measure of effect, for example, an RR or an OR. Generally, the farther from 1.0 (higher or lower) the RR or OR is, the greater the likelihood that the association is causal and the lower the likelihood that it is a result of bias or confounding. Measures of statistical significance, such as p values, are not indicators of the strength of an association but are rather measures of the probability of the results being due to random error.

Consistency

It is desirable to replicate the findings in different studies, that is, to observe an association in several studies done by different investigators in different populations using different study designs before drawing conclusions about the association. The more studies and types of studies in which the association has been observed, the more confident we are that the association is causal. However, consistency by itself is not sufficient evidence of an association. The committee considered findings that were consistently in the same direction (that is, the studies found predominantly positive or negative associations) among studies of different designs to be supportive of an association. It did not require exactly the same magnitude of association in different populations to conclude that there was an association. A consistent association could occur when the results of most studies were positive and the variations in measured effects were within the range expected to be due to random error.

Specificity of Association

Specificity of association is the degree to which an exposure (in this case, sustaining a TBI) is associated with a particular outcome. A positive finding is more convincing of causality when the association between the exposure and the outcome is specific to one or both than when the association is nonspecific to both. The committee recognized, however, that one-to-one specificity is not to be expected given the differences in type of injury, extent of injury, and locations of injury in the brain.

Temporal Relationship

If an observed association is real, exposure must have preceded the onset of an outcome. The committee considered whether the outcome occurred within some period after sustaining a TBI that was consistent with current understanding of the natural history of that outcome (to the extent that it was possible). It interpreted the lack of an appropriate sequence as evidence against causality but recognized that insufficient knowledge about the natural history and pathogenesis of many of the health effects under review limited the utility of this consideration.

Dose–Response Relationship

The existence of a dose–response relationship strengthens an inference that an association is real. However, the lack of an apparent dose–response relationship does not rule out an association. If the relative magnitude of exposure among several studies can be determined, indirect evidence of a dose–response relationship might exist. For example, if studies of presumably low-exposure cohorts (for example, mild TBIs or a single injury) show only mild increases in risk whereas studies of presumably high-exposure cohorts (for example, moderate to

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severe TBIs or repeated injuries) show larger increases in risk, the pattern would be consistent with a dose–response relationship.

Biologic Plausibility

Biologic plausibility reflects knowledge of the biologic mechanism by which a TBI could lead to a health outcome. That knowledge comes through mechanism-of-action or other studies, typically in animals. Biologic plausibility provides a high level of confidence in drawing a conclusion of "sufficient evidence of a causal association" (see below). However, a biologically plausible mechanism might not be known when an association is first documented.

Types of Observational-Study Designs

Epidemiologic-study designs differ in their ability to provide evidence of an association (Ellwood, 1998). It must be noted that the studies reviewed by the committee were seldom designed specifically to answer the question in the committee's charge, that is, whether sustaining a TBI during combat results in long-term adverse health outcomes. In examining the available epidemiologic studies, the committee addressed the question, Does the available evidence support a causal association between exposure (sustaining a TBI) and an outcome (a health effect)? Even a finding of a causal association between a TBI and a specific health effect does not mean that a TBI invariably results in the health effect or that all cases of the effect are the result of deployment. As discussed above, Hill's criterion of specificity is not particularly applicable in studies of TBI given the diffuseness of the injury, or even in injury epidemiology in general, and in any event such complete correspondence between exposure and effect is the exception in large populations (IOM, 1994). The committee evaluated the data and based its conclusions on the strength and coherence of the data that resulted from the selected epidemiologic studies that met its inclusion criteria.

The major types of epidemiologic studies that the committee considered were cohort studies, case–control studies, and cross-sectional studies. In each case below, *exposure*, for purposes of this study, means sustaining a TBI.

Cohort Studies

A cohort, or longitudinal, study follows a defined group, or cohort, over some period. It can test hypotheses about whether a TBI is related to the development of a health effect and can examine multiple health effects that may be associated with a TBI. Our review looked for evidence in cohort studies that compared health effects in people who had a TBI with effects in those who did not. The committee gave substantially less weight to cohort studies that included only persons with TBI and measured outcomes as a function of factors other than TBI, such as age. Those types of studies are valuable for determining risk factors other than TBI for specific outcomes, but they do not provide information on whether a particular outcome, such as Parkinson disease, is associated with TBI.

Cohort studies can be used to estimate risk difference, RR, and hazards, all of which measure the strength of an association. The risk difference is the rate of disease or other health effect in exposed persons minus the rate in unexposed persons; a rate greater than zero implies that extra cases of the effect are associated with the exposure. Relative risk is determined by

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dividing the rate of the effect in the exposed group by the rate in the unexposed group. An RR greater than 1 suggests a positive association between an exposure and an outcome, and a value less than 1 suggests a protective association. The farther the RR is from 1.0 (in either direction), the stronger the association

One major advantage of a cohort study is the ability of the investigator to define the exposure classification of subjects at the beginning of the study. Because participants are followed over time, it avoids problems with the temporal sequence between an exposure and an outcome; that is, it avoids the problem of effect–cause associations. Classification of exposure in prospective cohort studies is not influenced by the presence of a health effect, because the health effect has yet to occur, and this reduces an important source of potential bias known as misclassification bias (see later discussion). The disadvantages of cohort studies are the high costs associated with the use of a large study population, the long periods needed for followup (especially if the effect is rare), attrition of study subjects, and delay in obtaining results.

A prospective cohort study selects subjects on the basis of exposure (or lack of it) and follows the cohort to some date to determine whether and at what rate the outcome develops. A retrospective (or historical) cohort study differs from a prospective study temporally in that the investigator traces back in time to classify past exposures in the cohort and then tracks the cohort forward to the present to ascertain the rate of the outcome. The investigator often focuses on mortality from the outcome because of the relative ease of determining vital status of people and the availability of death certificates to determine the cause of death.

Standardized Mortality Studies

For comparison purposes, some cohort studies use mortality or morbidity rates in th general population because it might be difficult to identify a suitable group of unexposed people, especially if the outcome is rare. An example of this is the standardized mortality ratio (SMR), which is the ratio of the observed number of deaths in a cohort (from a specific cause, such as TBI) to the expected number of deaths in a reference population. An SMR greater than 1.0 generally suggests an increased risk of death in the exposed group. Such measures can also be used to examine morbidity, such as cancer.

The major problem in comparing rates in the general population with rates in military cohorts is the “healthy-warrior effect”. That effect arises when a military population experiences a lower mortality or morbidity rate than the general population, which consists of a mixture of healthy and unhealthy people. Inasmuch as military personnel must meet physical-health criteria when they enter the military and while they are on active duty, the group’s health status is usually better than that of the general population of the same age and sex. Since military personnel are at overall lower risk of adverse health outcomes compared to the general population, any excess risk associated with an exposure they experience must be large enough to overcome their inherent advantage in order to be detectable by such methods as SMR.

Case–Control Studies

In a case–control study, subjects (cases) are selected on the basis of having the outcome of interest; controls are selected on the basis of *not* having the outcome of interest. Investigators seek information on specific exposures. Cases and controls can be matched or not in the selection process with regard to such characteristics as age, sex, and socioeconomic status to suppress the influence of confounding variables in any observed differences. The odds of exposure to the

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agent in the cases are then compared with the odds of exposure in controls. An OR greater than 1 indicates that there is a potential association between the exposure and the outcome; the greater the OR, the greater the association. An OR less than 1 indicates that the exposure may protect against the outcome.

Case–control studies are useful for testing hypotheses about relationships between specific exposures and an outcome. They attempt to solve the problem of temporality by considering the order of exposure and outcome. They are especially useful and efficient for studying rare diseases and their associated exposures. Case–control studies have the advantages of ease, speed, and relatively low cost. They are also valuable for their ability to probe multiple exposures or risk factors. However, case–control studies are vulnerable to several types of bias, such as recall bias, in which cases are more likely to report exposures than controls, which can dilute or enhance an association between a health effect and an exposure. Other problems include identifying representative groups of cases, choosing suitable controls, and collecting comparable information on exposures in both cases and controls. The case–control study is often the first approach to testing a hypothesis about factors that might contribute to a specific health effect, especially a rare one.

A nested case–control study draws cases and controls from a previously defined cohort that was assembled for other purposes. Thus, it is said to be nested in a cohort study. Baseline data are collected when the cohort is identified; which to some degree avoids the problem of recall bias when the cases and controls are identified. Members of the cohort identified as having, for example, TBI serve as cases, and a sample of those who are TBI-free serve as controls. Baseline data on exposure in cases and controls are compared, as in a regular case-control study. Nested case–control studies are efficient in terms of time and cost in reconstructing exposure histories of cases and controls. In addition, because the cases and controls come from the same previously established cohort, concerns about selection bias are decreased.

Cross-sectional Studies

The main distinguishing feature of a cross-sectional study is that exposure and outcome data are collected at the same time. In a cross-sectional study, the strength of an association between an exposure and an outcome is measured as a prevalence ratio, or a prevalence OR. It might compare outcome or symptom rates between groups with and without TBI.

Cross-sectional studies are easier and less expensive to perform than cohort studies and can identify the prevalence of exposures and outcomes in a defined population. They are useful for generating hypotheses, but they are much less useful for determining cause–effect relationships, because collecting exposure and outcome data at the same time makes it impossible to establish which came first. Such studies are also subject to numerous other problems (Monson, 1990). Cross-sectional studies are of limited use for learning about symptom duration and chronicity, latency of onset, and prognosis.

INCLUSION CRITERIA

The committee's next step, after securing the full text of about 1,900 epidemiologic studies, was to determine which studies would be included in its review as primary or secondary

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(support) studies. To be included as a primary study, a study had to be a published in a peer-reviewed journal or have undergone an equally rigorous process, had to include details of its methods, had to include an appropriate reference or unexposed group, sufficient statistical power to detect an effect, had to have sufficiently representative followup to ensure external validity, and had to have used reasonable methods to control for confounders and to minimize systematic error. Studies also had to include identification of TBI in a population due to an external physical force rather than a degenerative or congenital condition and had to include long-term outcomes (6 months or longer). Secondary studies are studies that were less rigorous in their methods, and they carried less weight than primary studies. Of the 1,900 studies the committee read and evaluated, many did not meet the committee's criteria for inclusion and are not discussed in this volume.

Studies of patients with TBI due to malignancy, strokes, infection, ischemia, other diseases or disorders of the brain, intoxication, or oxygen deprivation were not considered. Additionally, the committee did not systematically review studies of children, the elderly, brain injured patients in litigation for compensation claims, case reports, or case series. Because the committee was charged with assessing only long-term outcomes, studies of outcomes not assessed beyond 6 months were excluded.

Methodologic Rigor

A study had to be a published in a peer-reviewed journal or other rigorously peer-reviewed publication, such as a government report, dissertation, or monograph; include sufficient methodologic details to allow the committee to judge whether it met inclusion criteria; include an unexposed control or reference group; have sufficient statistical power to detect effects; and use reasonable methods to control for confounders.

Exposure Assessment

For a study to be considered primary, the committee preferred studies that had an independent assessment of a TBI rather than self-reports of a TBI or reports by family members. It was preferable to have the TBI diagnosed or confirmed by a clinical evaluation, imaging, hospital record, or other medical record. However, unwitnessed self-reports of injury account for the bulk of the TBI literature, and the committee decided that it could not exclude such studies outright. In keeping those studies, the committee is well aware of the potential for misclassification of TBI due to recall bias.

Outcome (Health Effect) Assessment

The committee preferred studies that had an independent assessment of an outcome rather than self-reports of an outcome or reports by family members. It was preferable to have the health effect diagnosed or confirmed by a clinical evaluation, imaging, hospital record, or other medical record. For psychiatric outcomes, standardized interviews were preferred, such as the Structured Clinical Interview for DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders-IV-TR), the Diagnostic Interview Schedule, and the Composite International Diagnostic Interview; similarly, for neurocognitive outcomes, standardized and validated tests were preferred. Additionally, the outcome had to be diagnosed after sustaining the TBI.

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CONSIDERATIONS IN ASSESSING THE STRENGTH OF EVIDENCE

The committee's process for reaching conclusions about TBI and its potential for adverse health outcomes was collective and interactive. Once a study was included in the review because it met the committee's criteria, there were several considerations in assessing causality, including strength of the association, presence of a dose–response relationship, presence of a temporal relationship, consistency of the association, and biologic plausibility.

Categories of Association

The committee attempted to express its judgment of the available data clearly and precisely. It agreed to use the categories of association that have been established and used by previous Committees on Gulf War and Health and other Institute of Medicine committees that have evaluated vaccine safety, effects of herbicides used in Vietnam, and indoor pollutants related to asthma (IOM, 2000, 2003, 2005, 2006, 2007). Those categories of association have gained wide acceptance over more than a decade by Congress, government agencies (particularly the VA), researchers, and veterans groups.

The five categories below describe different levels of association and sound a recurring theme: the validity of an association is likely to vary to the extent to which common sources of spurious associations could be ruled out as the reason for the observed association. Accordingly, the criteria for each category express a degree of confidence based on the extent to which sources of error were reduced. The committee discussed the evidence and reached consensus on the categorization of the evidence for each health outcome in the various outcome chapters (Chapters 6–10).

Sufficient Evidence of a Causal Relationship

Evidence is sufficient to conclude that there is a causal relationship between sustaining a TBI and a specific health outcome in humans. The evidence fulfills the criteria of sufficient evidence of an association (below) and satisfies several of the criteria used to assess causality: strength of association, dose–response relationship, consistency of association, temporal relationship, specificity of association, and biologic plausibility.

Sufficient Evidence of an Association

Evidence is sufficient to conclude that there is a positive association; that is, a consistent association has been observed between sustaining a TBI and a specific health outcome in human studies in which chance and bias, including confounding, could be ruled out with reasonable confidence as an explanation for the observed association.

Limited/Suggestive Evidence of an Association

Evidence is suggestive of an association between sustaining a TBI and a specific health outcome in human studies but is limited because chance, bias, and confounding could not be ruled out with reasonable confidence.

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Inadequate/Insufficient Evidence to Determine Whether an Association Exists

Evidence is of insufficient quantity, quality, consistency, or statistical power to permit a conclusion regarding the existence of an association between sustaining a TBI and a specific health outcome in humans.

Limited/Suggestive Evidence of No Association

Evidence from several adequate studies, covering the full range of severity of TBIs that humans are known to encounter, is consistent in not showing a positive association between sustaining a TBI and a specific health outcome. A conclusion of no association is inevitably limited to the conditions, magnitudes of exposure (types of TBI—mild, moderate, and severe or penetrating), and length of observation in the available studies. The possibility of a very small increase in risk of the health outcome after sustaining a TBI cannot be excluded.

LIMITATIONS OF STUDIES

Many of the studies reviewed by the committee presented substantial obstacles to determining associations between TBI and long-term health outcomes because they were beset by limitations that are commonly encountered in epidemiologic studies, including lack of representative sample, selection bias, lack of control for potential confounding factors, self-reports of exposure and health outcomes, and outcome misclassification.

A study's representativeness, even if it is population-based, can be compromised by low participation rates and loss to followup. Low participation rates can introduce selection bias, for example, if people who are symptomatic choose to participate more frequently in studies than those who are not symptomatic. Similarly, loss to followup can result in attrition bias, a form of selection bias, particularly if attrition is associated with disease status. Researchers not only try to measure selection bias by comparing baseline characteristics of participants with nonparticipants or characteristics of those lost to followup with those followed but can make adjustments to estimate the magnitude and direction of its effects.

Some of the studies reviewed by the committee did not specify the time between the injury and the followup period, so the committee could not determine whether the outcome lasted longer than 6 months. Many studies involved populations in rehabilitation centers where subjects might have had multiple injuries that included TBI, but the initial TBI might have been due to a stroke or a brain tumor. Those studies presented several problems, such as lack of representativeness of the younger veteran population and an inherent selection bias; for example, they might include only people who have health insurance.

Most cohort studies rely on self-reporting of symptoms on questionnaires. Symptom self-reporting potentially introduces reporting or recall bias, which occurs when the group being studied reports what it remembers more frequently than a comparison group. Reporting bias can lead to overestimation of the prevalence of symptoms or diagnoses in the TBI population. Symptom self-reporting might sometimes introduce another type of bias known as outcome misclassification, which leads to errors in how symptoms are classified into outcomes and analyzed.

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Other limitations of the body of evidence are that studies might be too narrow in their assessment of health status, the measurement instruments might have been too insensitive to detect abnormalities that affect deployed veterans who had TBI, and the period of investigation might have been too brief to detect health outcomes that have a long latency or require many years to progress to the point where diagnosis, disability, hospitalization, or death occurs.

Apart from some large population-based studies of mortality after TBI and a few others of neurologic outcomes, many of the studies evaluated by the committee had small samples. When a study sample is too small, it is possible to miss clinically important differences. That is known as type II error. In such studies, attempts to examine even smaller subpopulations magnify the difficulties and reduce the likelihood of detecting meaningful differences. Of the studies examined by the committee, those with small samples were also sometimes hampered by other problems discussed above, including low participation rates, loss to followup, inadequate duration of followup, and self-reporting of symptoms.

An additional limitation of the studies under review is the lack of uniformity in defining the severity of TBI. Studies typically note whether the injury was a penetrating or a closed-head injury, but often used different criteria assess severity. Thus, the committee found it difficult to compare outcomes among studies, particularly in the "moderate" TBI category as researchers used different lengths of time of loss of consciousness (LOC) and of posttraumatic amnesia to define severity. Similarly, the range of scores on the Glasgow Coma Scale[1] was not always uniform in defining mild, moderate, and severe TBI.

The committee focused on studies of people who had sustained a TBI, that followed the subjects to determine long-term sequelae, and generally asked whether a specific outcome was more likely in people with TBI than in controls without TBI. The committee discussed characteristics of the optimal control group for such studies because the type of controls could influence inferences drawn from the studies examined. When the outcome was a medical condition or a social outcome, the committee considered the best comparison group to be controls with other traumatic injuries but without TBI (such as fractures) in the same facility as the subjects with TBI, because such controls permit examination of the effect of TBI on outcome independently of the general effects of trauma and of the common risk factors that lead to traumatic injury. When the outcome studied was death, the committee agreed that comparison with age- and sex-specific mortality in the general population provided the best comparison.

The committee found many studies that met its criteria for inclusion. However, many excellent studies were excluded from the review because they were not designed to answer the question posed to the committee, that is, What are the long-term outcomes associated with sustaining a TBI?

[1]The Glasgow Coma Scale (GCS) (Teasdale and Jennett, 1974) is a widely used scale to assess acute injury severity.

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5

MAJOR COHORT STUDIES

This chapter provides an overview of the major cohort studies identified by the committee that examined long-term health outcomes related to traumatic brain injury (TBI). The studies are categorized by population, including military and veteran populations, general population, and people who sustained sports-related TBIs.

Most major cohorts, once established, led to additional health outcome studies, which the committee refers to as derivative studies. Table 5-1, at the end of this chapter, provides information on each original cohort study, including the study design, the recruitment method, the eligible population, the study population, and the percentage of subjects who were enrolled. Information on the derivative studies appears in the table under the information on the original cohort studies from which they drew their populations and includes purpose, design, enrollment of subjects, sample size, response rates, and other characteristics if provided by the study authors. The information on derivative studies helped the committee to identify the populations that have been studied frequently and to understand which studies were independent of each other so that it could avoid evaluating studies of health outcomes in the same population repeatedly.

Studies discussed below might not be included as primary studies in Chapters 6 through 10, because they did not meet the committee's strict criteria for primary studies. However, many of those not included as primary studies have been included as secondary studies and informed the committee' decisions about the long-term consequences of TBI.

GENERAL LIMITATIONS OF COHORT STUDIES

A number of limitations were encountered when the committee was reviewing the studies that are detailed below. Among them are self-reporting of exposure and health outcomes, lack of representativeness, selection bias, and failure to include a reference or control population.

Many of the cohort studies relied on self-reporting of exposure (such as TBI, concussion, and loss of consciousness) and outcomes (such as headache and memory problems) rather than clinical evaluation or medical-record review. Self-reporting of exposure in retrospective cohort studies introduces the possibility of recall bias, the tendency for participants who have an outcome to overestimate (or underestimate) their exposure. That can limit the usefulness of study findings because outcomes may not necessarily be attributable to the exposure in question (TBI).

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Self-reporting of outcomes can introduce reporting bias. Reporting bias, which occurs when the group being studied reports more frequently what it remembers than a comparison group, can potentially lead to an overestimation of the incidence or prevalence of symptoms or diagnoses in the exposed populations. Self-reporting of outcomes based solely on symptoms might also introduce misclassification bias, in which there are errors in how symptoms are classified into outcomes.

Low participation rates, which can introduce selection bias, can severely limit the ability to generalize study results because the study population may not be representative of the larger population to which the results are meant to be generalized. A related issue is the use of inappropriate controls, such as comparison of military populations with civilian populations; military personnel may be healthier than the general population, so the two populations may be noncomparable. That is referred to as the healthy-warrior effect; there may have been nonrandom assignment of those selected and not selected for participation in the military. It is possible to measure the potential for such biases and to adjust for them in the analysis.

Another important limitation of some of the cohort studies is that they lack unexposed control groups. An unexposed group is a necessary component of a well-designed cohort study because it permits comparisons of rates of disease between exposed and unexposed populations and understanding of how an exposure affects the incidence of an outcome.

Some of the studies discussed below are registries of participants who presented for care. These studies are not intended to be representative of the symptoms and diagnoses of an entire population.

Although this is not necessarily a limitation, many studies discussed below were not designed with the committee's research question in mind. It was therefore difficult to use their findings to assess the broader question of the relation of long-term health outcomes to TBI.

ORGANIZATION OF THE CHAPTER

This chapter has sections on military cohort studies, population-based studies, other cohort studies, and sports-related studies. For each major cohort study, the methods for selecting the study population, the outcomes assessed, and the general findings are discussed. The committee was most interested in studies of long-term health outcomes related to TBI in military and veteran populations, so this group of studies is given primary consideration below.

MILITARY STUDIES

Studies of TBI have been conducted in nearly all the major conflicts of the 20th century, including World Wars I and II, the Korean War, and the Vietnam War; many of the studies evaluated seizure as the outcome of interest. Meirowsky and colleagues (1982) noted that studying military populations "offers the advantage of similarity in age and general health of the subjects at the time of injury and the relative ease with which they can be followed in subsequent years." The committee paid particular attention to studies that assessed TBI in military populations because these were generally long-term prospective assessments of the population of interest.

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E.A. Walker's Studies of Head-Injured Bavarian World War I Veterans

Walker and Erculei (1971) examined a cohort of head-injured Bavarian World War I veterans. The veterans were patients at a medical center established in Munich in 1916 for head injuries. Medical records, including field medical records and neurology reports on 5,500 men who had sustained head injuries were reviewed in 1964–1966. The records also included information on the men for up to 50 years after injury. About 1,000 records were randomly selected from the 5,500, and death certificates were sought from social-welfare offices in Bavaria and West Germany. Vital statistics were obtained for about 600 of the 1,000 men; the remainder could not be located. Controls were about 600 uninjured Bavarian World War I veterans. Men who were born before 1880, who died before the age of 35 years, or whose dates of death were not known were excluded. Head injuries were diagnosed on the basis of demonstration of immediate posttraumatic neurologic disturbance or evidence of a contusion, laceration, or compound wound injury of the scalp. Posttraumatic epilepsy was diagnosed on the basis of absence of preinjury seizures and the occurrence of seizures at some time after injury. Seizures were verified by a physician, nurse, or family member; if no outside party could verify the seizure occurred, this was noted. The authors noted that most of the patients had their first seizure within a year after the injury and others many years after the injury (Walker et al., 1971).

Walker and colleagues (1971) compared life expectancy of those with injuries and unwounded Bavarian veterans of World War I who had been awarded service medals carrying small pensions. The injured group had 1.8% more deaths than expected in the general male population, and a 4-year shorter life expectancy than the control group. In 1965, 73% of men at least 65 years old with TBI and 80% of those at least 65 years old without TBI were alive. Weiss et al. (1982) used the same data and found that in 1972, 497 (76.8%) of 647 TBI veterans and 483 (78.4%) of 616 of the control group had died.

E.A. Walker's Studies of Head-Injured World War II Veterans

Walker and Ercluei (1969) also conducted a cohort study of 364 severely head-injured World War II veterans 15 years after injury. Of these, 241 were originally studied at the Army Posttraumatic Epilepsy Center at Cushing General Hospital in Framingham, MA, in 1945–1946; these patients experienced at least one posttraumatic seizure. A battery of medical, psychologic, and electroencephalographic (EEG) tests were administered 1–3 years after injury; a 10-year followup consisted of examination, phone interview, or questionnaire. The authors reported that annual contact was made with nearly all subjects. The other 123, unselected head-injured men were studied as part of a followup in Baltimore from 1950 to 1954 and identified through Army and Veterans' Administration (VA) pension rosters; the population was comparable with the Cushing General Hospital group in severity of injury. Medical records were not as detailed and complete as those on the group described previously. Neurologic, social, psychometric, and EEG tests were administered 6–9 years after injury.

In general, the study participants had more severe brain wounds than would typically be seen in civilian or military hospitals. Dural penetrating frontal wounds tended to be included in the series although occipital and temporal injuries tended to be excluded (Walker and Erculei, 1969); dural penetration was found in 87% of the Cushing General Hospital group and in 71% of the Baltimore group (Walker and Erculei, 1970).

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The authors contacted participants by mail, and information was obtained through interviews and examination. They collected data on time from injury to examination, socioeconomic and work status, clinical symptoms, state of cranium and scalp, neurologic examination, epileptic status, EEG examinations, and psychometric testing (Wechsler-Bellevue, Minnesota Multiphasic Personality Inventory, Goddard Form Board, and McGill Picture Anomaly Test). Information was obtained on 343 (94%) of the 364 men originally identified; 31 died, leaving 313 living patients[2]. Of the 313, 243 (78%) were examined in person (Walker and Erculei, 1969).

The authors assessed a variety of outcomes related to head injury, including neurologic symptoms (nervousness, headache, and other posttraumatic symptoms, such as nervousness and headache), posttraumatic epilepsy, employment status and other social-function outcomes, and psychologic outcomes. Of the 313 men, 212 (68%) reported some form of nervousness, from mild to severe, and 200 (64%) reported that they had experienced headaches. The authors also assessed posttraumatic syndrome, defined as a complex of symptoms that follow a minor head injury, including dizziness, nervousness, anxiety, and emotional instability. Of the 306 veterans on whom information was available, 34 (11%) reported no complaints, 65 (21%) had isolated symptoms, and 207 (68%) had posttraumatic syndrome (Walker and Erculei, 1969).

Walker and colleagues (1969) also studied the prevalence of posttraumatic epilepsy. Two primary groups were defined for the analysis: 199 posttraumatic epileptic men from Cushing General Hospital and 114 men with posttraumatic encephalopathy from the Baltimore group who were matched by class of injury. Clinical examinations were conducted on 154 of those with epilepsy and 95 of those with encephalopathy. The authors found a statistically significantly lower survival rate in those with posttraumatic-epilepsy. Patients with posttraumatic epilepsy were more likely to be unemployed (57%) than those with posttraumatic encephalopathy (14%). Similarly, neurologic deficits were more likely in the group with epilepsy than in the group with encephalopathy. Hemiplegia, for example, was found in 64% of the men with epilepsy and 40% of those with encephalopathy. Increased mental impairment was also noted in the epileptic group; in the memory tests, two errors or fewer were recorded by 85% of the posttraumatic-encephalopathy group and 66% of the epilepsy group. Walker and Erculei (1970) also assessed post-traumatic epilepsy and found that 15 years postinjury, 40% (n = 92) had no seizures of any time between the fifth and fifteenth year; three percent had no seizures from the 10th to 15th year. Twenty-three percent or 52 men continued to have 1 to 6 episodes annually; 68 had more than 6 episodes per year.

In another analysis, Walker and colleagues (1969) assessed employment status after head injury in 303 subjects (nine were omitted because they were hospitalized during the followup assessment) and found that 182 (60%) men were regularly employed and 121 (40%) were unemployed or working irregularly.

Neurologic deficits were also assessed (Walker and Erculei, 1969). Of the 249 men examined, 199 (80%) exhibited abnormality of neurologic function. Of those with abnormal neurologic function, hemiplegia was present alone or in combination with other findings in 118 (59%), hemianesthesia in 121 (61%), hemianopsia in 43 (22%), aphasia in 36 (18%), mental impairment in 13 (7%), and cranial nerve defect in 137 (69%).

[2] Numbers as reported in study.

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Walker and Erculei (1969) found that few of the patients who had psychologic conditions in the early posttraumatic years recovered, 19 men developed mental abnormalities 10–15 years after injury, and severe mental disturbances occurred in only a small percentage of the patients.

Finnish Studies

Since 1948, the treatment, rehabilitation, and study of all head-injured Finnish war veterans have been monitored by one central institution, the Rehabilitation Institute for Brain-Injured Veterans. Achte and colleagues (1969), in an uncontrolled series, followed 3,552 men who suffered head injury in the Finnish wars of 1939–1945 to identify the prevalence of posttraumatic psychoses that developed up to 22–26 years after injury. On admission, mild injuries accounted for 19%, moderately severe for 59%, and severe for 22% of the sample; open head injuries were present in 42% of patients. Patients' initial medical records and examination and treatment records were reviewed to ensure the presence of a brain injury; questionable cases were excluded. In addition, moderate and severe injuries may have been overrepresented inasmuch as patients with mild traumas were often left untreated. Most patients were examined personally by the authors; otherwise, records of psychiatric treatment were obtained in addition to personal communication with the patients. Between the time of injury and 1966, 317 (8.9%) of the original population experienced at least one psychotic episode; schizophrenic psychosis was the most prevalent at 21.1% of the 317 (it appeared to be more frequent in the mildly injured and those under 20 years old), followed by paranoid psychosis (17.6%), epileptic psychosis (14.6%), and concussion psychosis (13.7%). Psychosis began in 24.0% of the cases less than 1 year, in 16.0% 1–5 years, in 17.7% 5–10 years, and in 42.3% over 10 years after injury.

In a more inclusive series by Achte and colleagues (1991), roughly 10,000 Finnish veterans were followed for 50 years after brain injury. Of them, 2,907 suffered some type of psychiatric disturbance throughout their lives, 26% (762) of which were classified as psychotic. At the time of study publication, 251 of those veterans were assigned a detailed diagnosis with the following distribution: delusional psychosis, 28%; major depression, 21%; delirium, 18%; and paranoid schizophrenia, 14%. Delusional psychosis tended to develop 15–19 years after injury and persisted for over 5 years in 40% of cases; paranoid schizophrenia and schizophreniform generally had a shorter latency—less than a year in 23% of cases—and persisted for over 5 years in 63% of cases.

Teuber's Cohort

In the late 1940s and 1950s, Teuber and colleagues at the New York University–Bellevue Medical Center recruited and examined over 300 World War II veterans (and some from World War I and the Korean War) who lived near New York City and had sustained penetrating injuries of the brain or the peripheral nervous system (Weinstein, 1954). All the veterans in this longitudinal cohort study, originally identified from rosters maintained by the VA, incurred traumatic lesions in the service. Sensory, motor, and cognitive tests were administered to the veterans, first in Teuber's New York laboratory and later by investigators at the Massachusetts Institute of Technology.

In one early study by Teuber and Weinstein (1954), 35 brain-injured veterans and 12 controls with arm or leg peripheral nerve injury were selected for assessment of performance on a modified Seguin-Goddard formboard task by area of brain injury. The brain-injured veterans

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made significantly more errors, recalled fewer forms, and had greater variability in the time it took to place the correct form in the correct opening. The investigators did not observe greater impairment in those with frontal lobe injuries than in those with lesions in the parietal, temporal, or occipital lobes.

In another study, Weinstein and Teuber (1957a) obtained preinjury scores on the Army General Classification Test (AGCT) for 62 men who subsequently sustained penetrating brain injuries and 50 controls who incurred nerve injuries of the arm or leg. Both groups of men were retested with a comparable form of the AGCT (First Civilian Edition). The preinjury scores of the two groups were similar: the mean score was 106.4 in the controls and 105.0 in the brain-injured group. Scores on the postinjury test showed some gains in the controls (48 of the 50 controls increased their mean scores to 119.4) while there was little or no change in the brain injured men's test scores. In the same sample of veterans, Weinstein and Teuber (1957b) reported that the findings were independent of any effects for differences in preinjury education and preinjury AGCT score.

A study of roughness discrimination was also conducted with Teuber's cohort (Weinstein et al., 1958), in which 43 veterans with brain injury were compared with 20 controls with leg peripheral nerve injuries. The study participants' task was to touch a patch of sandpaper and then attempt to find in a comparison array of 18 patches the one that was identical in roughness. Four sets of experiments were conducted: unilateral-successive for ipsilateral hand, unilateral-successive for contralateral hand, bilateral-successive, and bilateral-simultaneous. In all groups, there was a significantly lower average error in the unilateral experiments. However, there was a deficit in roughness discrimination in veterans who had sustained a penetrating brain injury. Under unilateral testing conditions, the left hand appeared to be more vulnerable to error than the right hand, regardless of the location of the brain injury.

In more recent studies by Corkin et al. (1984, 1989), the investigators examined whether life expectancy or cognitive decline late in life is associated with having survived a penetrating brain injury. To study factors that might influence life expectancy, the authors evaluated 190 men who had sustained a brain injury during World War II and 106 men who had sustained peripheral nerve injuries during the war. Survival information was obtained from the VA, and the Kaplan–Meier method was used to estimate cumulative survival distributions for the two groups. Although sustaining a penetrating head injury alone did not shorten life expectancy, the risk of death increased when it was coupled with posttraumatic epilepsy. As of May 1, 1983, mortality was 3.6 times higher in veterans with brain injury and epilepsy than in veterans with peripheral nerve injury.

Corkin et al. (1989) also evaluated the interaction between aging and effects of brain injury in a similar series of veterans. To study whether head injury exacerbates cognitive decline in later years, the authors evaluated 57 World War II veterans with head injury and 27 with peripheral nerve injury matched on age, premorbid intelligence, and education. The participants received two timed cognitive tests: the ACGT (Total, Vocabulary, Arithmetic, and Block Counting) and the Hidden Figures Test, in which participants trace a simple geometric figure embedded in another geometric figure. On all five cognitive measures, the group with brain injury was statistically significantly inferior to the control group 10 years after injury. Over another 30-year period (that is, 40 years after injury), cognitive decline was observed in the brain-injury group on every AGCT measure except Vocabulary as compared to the control group (Corkin et al., 1989).

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W.F. Caveness Studies of Korean War Veterans

In 1951, W.F. Caveness, then chief of the neurologic service in the US Naval Hospital, in Yokusaka, Japan, initiated a study of craniocerebral injuries in male military personnel wounded during or immediately after the Korean War. The participants were seen at Yokusaka or in the US Navy hospital ships off the coast of Korea. The investigators identified 467 cases in 1951–1954, many of them in Navy or Marines Corps personnel. During the initial period, investigators conducted a review of medical records, gave periodic physical examinations, distributed supplemental questionnaires and personal letters, and conducted interviews. The head injuries were categorized as related to missiles (resulting from contact with small-arms fire, grenades, land-mine mortar, or heavy artillery) or not related to missiles (resulting from blunt or sharp objects or vehicle accidents or secondary to blast); missile-related injuries accounted for more than half the injuries in the cohort (Caveness, 1963).

A followup study was conducted 8–11 years after the initial injury. During the followup period, 356 of the original cases participated (76% of the total and 87% of those eligible for followup). Information was collected with a mailed questionnaire, a physical examination, interviews with the American Red Cross, and review of VA records. During the period 1957–1958, additional VA information was available on 85% of the participants. Questionnaires were obtained in 1961–1962 from 91% of the participants, personal letters from 22%, and telephone replies from 10% (Caveness, 1963).

Additional studies of this cohort evaluated the prevalence of posttraumatic epilepsy as diagnosed by EEG. Seizures were diagnosed if they fulfilled the criteria for focal somatomotor, somatosensory, special sensory, or adversive seizures. Other less well-defined focal events, such as patterns attributed to the temporal lobe, were included if accompanied by other overt phenomena of seizures (Caveness, 1963). The investigators noted that generalized seizures, characterized by a loss in consciousness with or without bilateral motor expression, “were recognized either as a progression from a focal onset, in conjunction with focal seizures, or as a principal expression of the convulsive disorder”.

Evans (1962) evaluated the prevalence of seizures in 422 of the head-injured Korean War veterans 3–11 years after injury. The authors found the overall prevalence of seizures to be 19.7%. Those with penetrating head injuries had a prevalence of seizures of 32%, those with blunt head injuries 8%, and those with blast wounds 2%.

Caveness and colleagues (1962) assessed the prevalence of seizures in five retrospective cohorts from three wars (World War I, World War II, and the Korean War). In a random sample of 407 cases from the Korean War 5 years after injury, 24.1% had seizures—35.1% of those with missile head wounds and 12.2% with blunt or blast wounds.

Caveness (1963) also found that 8–9% of the 467 men initially included in the study population had seizures within the first 2 weeks. Of the 356 men followed up 8–11 years after injury, 109 (30.6%) had seizures. Forty-two percent of those with penetrating head wounds and 16.4% with blunt head wounds had seizures. There was no significant difference in seizure incidence between the total original group and those followed for 8–11 years.

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Vietnam Head Injury Study

The Vietnam Head Injury Study (VHIS) is a long-term, prospective followup study of head-injured Vietnam veterans, originally organized by William Caveness at the National Institutes of Health (NIH). The ultimate goal of the study is to evaluate the long-term neuropsychologic and other health outcomes of patients with penetrating head injury to learn about the role of head injury in the etiology of dementia and posttraumatic epilepsy, mechanisms of motor and cognitive recovery, and functions of various regions of the brain. The initial registry phase, conducted during the Vietnam War, consisted of military physicians' entering demographic, injury, and outcome data on registry forms for about 2,000 head-injured soldiers who had survived the first week after sustaining injury. Data were entered during 1967–1970. Over 95% of the patients enrolled were male, had penetrating head injuries, and were 18–25 years old (Grafman, 2007).

Phase I of the study was a detailed medical-records review conducted some 5 years after injury. At that time, the VHIS cohort consisted of 1,200 men who had either closed or penetrating head injuries. Field records and records of acute hospitalization, rehabilitation, and followup were available for all subjects. The VHIS cohort allowed tracking over long followup periods and included preinjury vocational and intelligence testing (National Naval Medical Center, 2008).

Phase II, conducted primarily by Grafman and Salazar, was a collaborative effort of the VA, NIH, and the American Red Cross and consisted of a comprehensive inpatient evaluation at the Walter Reed Army Medical Center of 520 head-injured subjects from the original cohort of 1,200 and 85 matched normal controls who were evaluated in 1981–1984 (12–15 years after injury) (National Naval Medical Center, 2008). The controls were recruited from the VA files of non–head-injured soldiers who had served in Vietnam in the same years and were within the same age range as the head-injured soldiers. Many patients were lost to followup and were no longer receiving medical care or were not honorably discharged, because of behavioral changes related to their head injuries. Phase II was also used to identify these patients and refer them for appropriate medical care. During phase II, researchers conducted a number of tests of neurologic, motor, speech and language, and neuropsychologic outcomes. Phase II also identified veterans with specific lesions (such as orbitofrontal and dorsal frontal) or with particular cognitive or neurobehavioral deficits and studied the prevalence of posttraumatic epilepsy and cognitive function after head injury (National Naval Medical Center, 2008).

Two such studies in phase II assessed seizures after head injury (Swanson et al., 1995), and (Salazar et al., 1985). Swanson and colleagues (1995) assessed interictal personality traits in 238 veterans who had developed seizure disorders and compared them with personality traits in 229 veterans with penetrating head injuries but without seizures and 84 uninjured controls. Of the 238 with seizure disorders, 39 had simple partial seizures, 59 had complex partial seizures, 76 had partial seizures with secondary generalization, and 64 had generalized seizures. The authors assessed history of psychiatric treatment, preinjury intelligence, brain-volume loss, seizure frequency, and duration of epilepsy. Statistically significant increases in interictal psychopathology were observed in the groups with complex partial seizures, partial seizures with secondary generalization, and generalized seizures (but not simple partial seizures) compared with controls. No group differences between groups with seizure types were found.

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In an evaluation of 421 veterans from the VHIS cohort, Salazar and colleagues (1985) found that 53% had posttraumatic epilepsy. The relative risk of epilepsy in the head-injured veterans was 580 times higher than that in the general age-matched population in the first 6 months after injury and fell to 25 times higher after 10 years. Hemiparesis ($p = 0.03$), organic mental disorder ($p = 0.015$), aphasia ($p = 0.009$), headache ($p = 0.001$), and visual-field loss ($p = 0.015$) were associated with seizures. The authors found that the incidence of posttraumatic epilepsy was 86% in patients who had residual aphasia. Of patients with seizures, 57% had attacks within a year and 25% 1–5 years after injury; in about 18%, the first seizure occurred more than 5 years after injury; and in 7%, the first seizure occurred 10 years or more after injury. Patients with frequent seizures in the first year after injury were more likely to have a longer duration of epilepsy ($p < 0.001$). Of all those who sustained head injuries, 28% had persistent seizures 15 years after injury. The major limitations of the study include its lack of a reference group. It is also unclear whether seizures occurred before head injury.

Phase III, conducted from 2004 to 2006, examined the role of head injury in cognitive neuroplasticity of the aging brain, memory and amnesia, such neurologic disorders as epilepsy, and social functioning. Phase III testing included elective neuroimaging, such as positron-emission tomography, and quantitative EEG. Of the 520 patients in phase II, 182 (35%) participated in phase III, and 17 were newly recruited. Of the 85 controls in phase II, 32 (38%) participated in phase III, and 23 were newly recruited (Grafman, 2007).

Two studies from phase III have been published: TBI and cognitive outcomes and TBI and PTSD. Raymont and colleagues (2008) studied the relationship of preinjury intelligence, brain-tissue volume loss, lesion location, demographic variables, and the role of genetic markers in long-term cognitive decline. They found that subjects with penetrating head injury had a greater degree of overall cognitive decline than controls. Preinjury intelligence was the most consistent predictor of cognitive outcomes. Koenigs and colleagues (2007) studied the relationship between TBI and posttraumatic stress disorder (PTSD) and found a "reduced occurrence of post traumatic stress disorder . . . following ventromedial prefrontal cortex damage and the complete absence of PTSD following amygdala damage".

Phase IV will begin in 2015, about 45 years after injury. The VHIS will provide baseline premorbid and injury information that can be used to asses the effects of penetrating head injury on the development of a variety of neurologic disorders in old age, the rate of physical and cognitive decline, and the effects of various variables on performance data. The investigators will re-examine the patients on some of the tasks (including standardized tests and the Armed Forces Qualification Test) administered during the phase II evaluation to assess cognitive, mood, personality, and neurologic functions.

Vietnam Experience Study

The Vietnam Experience Study (VES) was a multidimensional health assessment that began with data collection from Vietnam-era veterans in the middle 1980s, about 16 years after discharge (Luis et al., 2003). The VES included four components: medical and psychologic examinations, mortality assessments, telephone interviews, and reproductive-outcome assessments (CDC, 1989). The eligible population consisted of male US Army veterans who first entered the military during the period January 1965–December 1971, served at least 4 months on active duty, served only one tour of duty, obtained a military occupational specialty, and

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achieved a pay grade no higher than E-5 (sergeant) on discharge. On the basis of those requirements, random sampling of military records found 9,324 men who had been members of the US Army and served a single tour in Vietnam and 8,989 who served elsewhere (CDC, 1989). From the total eligible population, 4,462 veterans were randomly selected. A comprehensive 3-day medical and psychologic evaluation was administered to ascertain what health-related events occurred from time of military discharge to the study date (Luis et al., 2003). Numerous studies were published on the basis of extracted data on the cohort; the three described below evaluate the effects of mild TBI.

Luis and colleagues (2003) compared the prevalence of persistent postconcussion symptom complex (PPCSC) in veterans with and without a history of mild TBI. Of the 4,462 randomly selected veterans, 329 were excluded because they met criteria for PPCSC in the 10th edition of the International Classification of Diseases (ICD-10) or in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) but not both; 55 were excluded because of hospitalization, and 121 were excluded because data on them were incomplete. The remaining 3,957 were categorized as follows: 2,937 with no history of motor-vehicle accident (MVA) and no history of TBI, 488 with a history of MVA but no history of TBI, 323 with a history of TBI unaccompanied by loss of consciousness (LOC), and 209 with a history of TBI accompanied by LOC. Results indicated that the group that had had TBI with LOC had significantly greater odds of having PPCSC than the unexposed control group (odds ratio [OR], 2.84; 95% confidence interval [CI], 2.12–3.80). No significant difference was found between the group with a history of an MVA but no TBI and the group with TBI but no LOC. Multiple factors (demographic, psychiatric, and social support) accounted for 33% of the variance in PPCSC in participants with TBI (history of TBI with or without LOC), but significantly less variance was found in the no-TBI group (23.9%).

Vanderploeg and colleagues (2007) used a cross-sectional cohort sample to examine the long-term psychiatric, neurologic, and psychosocial outcomes resulting from self-reported mild TBI. A subsample of 4,384 veterans (excluding 40 who were hospitalized after injury and 38 on whom data were incomplete) were categorized into three groups: no history of MVA and no history of TBI (normal control, 3,214, 73%), injured in an MVA but no history of TBI (MVA control, 539, 12.3%), and TBI with altered consciousness (mild TBI, 254, 5.8%); those who reported a TBI without LOC were excluded (n=377, 8.6%). Age, education, enlistment General Technical Test scores, and medical and psychiatric conditions varied among the three groups and were statistically controlled for in later analyses. The mild-TBI group had higher odds of having depression than the normal control group (OR, 1.77; 95% CI, 1.13–2.78). Antisocial personality disorder was twice as prevalent in the veterans with mild TBI as in the normal control group, but this outcome probably reflects a risk factor for obtaining an injury, given the similar rates of preinjury conduct disorder. The odds of postconcussion symptoms (PCS) were about doubled in patients with a history of mild TBI by both DSM-IV and ICD-10 criteria (OR, 2.00 and 1.80, respectively; 95% CI, 1.49–2.69 and 1.33–2.43, respectively). The odds of peripheral visual imperceptions were twice as high (OR, 1.98; 95% CI, 1.21–3.24) and of impaired tandem gait were about 3 times as high (OR, 2.93; 95% CI, 1.34–6.38). People with TBI had higher odds of being unmarried (OR, 2.01; 95% CI, 1.57–2.75) and higher odds of employment issues (OR, 1.89; 95% CI, 1.36–2.64), low income (OR, 1.88; 95% CI, 1.29–2.74), and self-reported disability (OR, 2.90; 95% CI, 1.63–5.15).

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Vanderploeg and colleagues (2005) used the same cohort to conduct a cross-sectional study of neuropsychologic outcomes. A full 15-measure neuropsychologic battery with neurologic measures of tandem gait and peripheral visual attention was administered. Results revealed no statistically significant difference in any of the measures among the three groups. In examining more subtle differences in attention, concentration, and memory, it was found that the mild-TBI group had significantly higher odds of being unable to continue the Paced Auditory Serial Addition Test (PASAT) than either of the two control groups (comparison with normal control group: OR, 1.32; 95% CI, 1.00–1.73; comparison MVA control, OR, 1.53; 95% CI 1.10–2.13). With respect to working memory, the mild-TBI group had excessive proactive interference (comparison with normal control group: OR, 1.66; 95% CI, 1.11–2.47). PASAT continuation problems were associated with left-side visual imperceptions, and excessive proactive interference was associated with impaired tandem gait in the mild-TBI group.

In another study of the VES cohort, Vanderploeg and colleagues (2003) conducted logistic regression analyses to survey long-term outcomes of work and marital status in people who had mild TBI and any pre-existing factors that may perpetuate the symptoms of the injury. The author notes that the subsample (after exclusion of 53 people because they were hospitalized and 87 because data on them were incomplete) consisted of 4,322 people: 626 (14%) who had a mild TBI (373 without LOC, and 253 with LOC) and 3,896 (86%) who did not have a TBI. Psychiatric disorders were assessed with the Diagnostic Interview Schedule (DIS-II-A), and psychosocial outcomes were gathered by trained examiners. Results indicate that the outcome of a mild TBI may be influenced by the presence of any pre-existing demographic, medical, or psychiatric factors. Factors associated with work and marital status accounted for 23% and 17%, respectively, of the variance in those with head injury. Variance was significantly lower in those without head injury: 13.6% and 9.4%, respectively.

POPULATION-BASED STUDIES

Rochester Epidemiology Project

The Rochester Epidemiology Project is a medical-records–linkage system that encompasses detailed health-care information on residents of the City of Rochester and Olmsted County, Minnesota. Funded initially in 1966 with medical records dating back to 1910, the project was designed to link all medical data and clinical information developed by the Mayo Clinic with data obtained by community health providers, including Olmsted Medical Group, the Olmsted Community Hospital, the University of Minnesota Hospital, and the Minneapolis VA Medical Center. Each patient was assigned a unique identifier, and information on all medical visits has been recorded for each patient. The database includes thorough medical histories, clinical assessments, consultation reports, surgical procedures, laboratory and radiology results, death certificates, and autopsy reports (Flaada et al., 2007). The medical information is continuously updated into an electronic format. By maintaining complete medical histories, the Rochester Epidemiology Project provides the capability to conduct population-based studies of disease risk factors and health outcomes and can be used to study long-term secular trends in disease incidence (Melton, 1996). As of 1996, the project included medical records on a population with more than 3.6 million person-years of experience in 1950–1995 (Melton, 1996). The demographic characteristics of Olmsted County residents largely resemble those of the US white population (Melton, 1996). Over 1,500 publications have resulted from the project,

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including studies related to TBI and a variety of health outcomes, such as seizures, Alzheimer disease, and Parkinson disease.

A number of studies evaluated the incidence of seizures after head trauma in this population. In 1980, Annegers and colleagues conducted a retrospective population-based cohort study to determine the risk of posttraumatic seizures in people in the Rochester Epidemiology Project who had sustained head injuries. The authors found that the risk of posttraumatic seizures after severe injury was 7.1% within 1 year and 11.6% within 5 years. In 1995, Annegers and colleagues assessed the incidence of seizures in the same population, including cases in 1935–1984. The age-adjusted incidence from 1955 to 1984 was 39/100,000 person-years. The age-adjusted incidence was higher in men (52.0) than in women (29.5). A third study conducted by Annegers et al. (1998) evaluated seizure cases in 1975–1984 with a followup period through 1994. The overall standardized incidence ratio (SIR) of seizures in patients with brain injury was 3.1 (95% CI, 2.5–3.8). The SIR was 1.5 (95% CI, 1.0–2.2) in those with mild TBI, 2.9 (95% CI, 1.9–4.1) in those with moderate TBI, and 17.0 (95% CI, 12.3–23.6) in those with severe TBI.

Studies of a number of neurodegenerative diseases—including Alzheimer disease, Parkinson disease, and multiple sclerosis—were also conducted. Bower and colleagues (2003) assessed the risk of Parkinson disease in the head-injured people and found that for any head trauma the odds of developing Parkinson disease were 4.3 (95% CI, 1.2–15.2); subjects who had a mild head injury with LOC or a more severe trauma had odds of 11.0 (95% CI, 1.4–85.2). Williams and colleagues (1991) assessed the risk of Alzheimer disease, dementia, and Parkinson disease in the same head-injured population and found that the standardized morbidity ratio was 1.00 (95% CI, 0.63–1.50) for Alzheimer disease, 1.06 (95% CI, 0.74–1.46) for dementia, and 0.94 (95% CI, 0.38–1.94) for Parkinson disease. Siva and colleagues (1993), using data from the Rochester Epidemiology Project, identified an incidence and prevalence cohort with multiple sclerosis (MS), a head-injury cohort, and a lumbar-disk–surgery cohort to evaluate the association between mechanical trauma and MS onset or exacerbation. Of a cohort of 819 people with head injury in Olmsted County, none developed multiple sclerosis within 6 months of the trauma. Of a lumbar-disk–surgery cohort of 942 local residents, five developed MS, but onset of the disease preceded the spinal surgery in four of the five. The authors found no association between head injury or lumbar-disk surgery and the onset of MS.

Brown et al. (2004) carried out a study to determine whether mortality from TBI was affected by the severity of the injury and the survival time by using medical records from the Rochester Epidemiology Project. There were 68 deaths in the moderate-to-severe–TBI group for a Kaplan–Meier estimated 30-day case-fatality rate of 29.3%. During the followup period, the 68 deaths demonstrated a significantly higher risk of mortality as compared to the 1990 Minnesota white population (risk ratio, 5.29; 95% CI, 4.11–6.71); but in people with moderate or severe TBI who survived for 6 months after injury, the risk ratio for death was not significantly greater than the expected (14 deaths vs 12.7 expected; risk ratio, 1.10; 95% CI, 0.60–1.85). Findings in those with mild TBI were similar.

Community-Based Study of Injuries in the Aquitaine, France

A population-based prospective study was conducted over a 1-year period from 1985 to 1986 in the Aquitaine, France, to assess the incidence, causes and severities of injuries. The Aquitaine, one of the 22 administrative regions in France, contains both urban and rural areas.

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The population in 1986 (extrapolated from the 1982 census) was estimated at 2.7 million. The cases were people with unintentional or intentional injuries sustained from December 1985 to December 1986 that resulted in death or required hospitalization. Public and private hospitals participating in the study were asked to complete a questionnaire for each injury case that required admission. The questionnaire included queries about demographic information and time and place, cause, origin, and clinical nature of the injury. Causes and clinical nature of the injuries were coded according to a classification system designed specifically for the study. All 21 public hospitals and 38 of the 43 private hospitals contributed to the study (Tiret et al., 1989).

From 1985 to 1986, there were 391 deaths and 2,116 hospital admissions due to head trauma; the case-fatality rate was 4%. In the nonfatally head-injured patients, 80% of the head injuries were classified as mild, 11% moderate, and 9% severe (Tiret et al., 1990). The overall annual incidence was 281 per 100,000, and the annual mortality was 22 per 100,000 (Tiret et al., 1990).

Masson and colleagues (1996) assessed the effects of cognitive, behavioral, and somatic impairments on disability and recovery after TBI. The study population included 231 TBI patients 5 years after injury and 80 lower-limb–injured controls. Sixty-four lower-limb–injured patients and 176 TBI patients were assessed. The severity of the head injuries was defined as severe if a patient had a Glasgow Coma Scale (GCS) score of 8 or less for at least 6 hours in the first 24 hours after injury; moderate if the patients had one of the following, a GCS score of 8 or less between 1 and 6 hours, a GCS score of 9–12 on the first day after injury, an abnormal computed tomography scan, or a need for a neurosurgical procedure; and minor if neither of those categories was appropriate. A number of complaints were more commonly reported in TBI patients than in the lower-limb–injured patients, such as headache (OR, 4.6), memory problems (OR, 4.01), dizziness (OR, 3.35), anxiety (OR, 6.11), and sleep disturbance (OR, 3.10). Regarding mild, moderate, and severe TBI, there was no significant difference in the prevalence of headaches (44%, 54%, 44%), anxiety (47%, 49%, 63%), and dizziness (33%, 37%, 26%) among the three TBI severity groups, respectively. Mental impairments were reported frequently in patients with severe TBI (18–40% of patients); however, most impairments in patients with minor and moderate TBI were related to associated injuries.

Masson and colleagues (1997) conducted a study to assess long-term disabilities related to TBI in 407 patients. The authors found that 5 years after injury 64 of the patients had died and 36 were lost to followup. Of those who sustained severe head injury, 56% died, and 50% of the survivors were disabled. The authors note that "head injuries induce long-lasting handicap in 9 per 100,000 habitants which is severe in 2 per 100,000."

Canadian Study of Health and Aging

The Canadian Study of Health and Aging (CSHA) is a population-based cohort study designed to assess the prevalence and incidence of dementia and risk factors for it in the Canadian population. Planned originally in 1989, the CSHA includes people 65 years old and older sampled from 36 communities around the country. The study population was selected to be representative of the general population (Lindsay, 2002).

The study was conducted in three phases: CSHA-1 in 1991–1992, CSHA-2 in 1996–1997, and CSHA-3 in 2001–2002 (studies of which were not directly applicable to this report). Initial contact with study participants was made by telephone, and they were asked questions

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about current health issues. Participants who were living in long-term-care institutions were given a clinical examination. Those living in the community were interviewed in their homes and then screened for dementia. A community interview was held to discuss general health issues, disability, and the presence of chronic ailments. Screening tests for cognitive impairment were administered, including the Modified Mini-Mental State Examination. A person who screened positive for impairment was asked to participate in a clinical examination; independent diagnoses were also made by a physician and a neuropsychologist.

The clinical examination included neuropsychologic tests and medical assessment to permit a preliminary diagnosis of dementia. The diagnoses were the basis of the incidence and prevalence rates and were used in followup studies to identify risk factors. Followup studies included the same diagnostic criteria; cases were reassessed to be diagnosed according to new criteria based on the DSM-IV.

In CSHA-1, 10,263 participants were identified; 9,008 lived in the community, and 1,255 lived in institutions. Participants who were included were interviewed about health issues and limitations in performing basic daily-life activities as assessed by the Older Americans' Resources and Services Activities of Daily Living Scale (Lindsay et al., 2002).

A case–control study was conducted to assess risk factors associated with Alzheimer disease or other dementias (CSHA, 1994). The participants were given a questionnaire that included questions about family and medical history, behavior, occupational and environmental exposures, and lifestyle. To avoid recall bias, questionnaires for participants with dementia were given to persons who knew them well. The study included 258 patients with probable Alzheimer disease, 129 with vascular dementia, and 535 normal controls. All participants who did not have cognitive impairment during this first phase were asked to complete a risk-factor questionnaire; these included 6,628 participants without cognitive impairment. A case–control study based on data from CSHA-1 (CSHA, 1994) found that age, family history of dementia, educational level, arthritis, and use of nonsteroidal anti-inflammatory drugs were significantly related to Alzheimer disease.

In 1996–1997, the subjects who had agreed to participate in CSHA-2 were interviewed to determine changes in health status during the prior 5 years and underwent a process similar to that in CSHA-1. During CSHA-2, investigators conducted a nested case-control study of 194 participants who had recently diagnosed Alzheimer disease and 3,894 controls. For vascular dementia, 105 newly diagnosed cases were compared with controls (Lindsay et al., 2002). The authors found that increasing age, fewer years of education, and the apolipoprotein e4 (APOE 4) allele were significantly associated with increased risk of Alzheimer disease. However, they found no statistically significant association between Alzheimer disease and family history of dementia, history of depression, sex, estrogen-replacement therapy, head trauma, antiperspirant or antacid use, smoking, high blood pressure, heart disease, or stroke.

Traumatic Brain Injury Model Systems

The Traumatic Brain Injury Model Systems (TBIMS) program was established in 1987 by the National Institute on Disability and Rehabilitation Research of the US Department of Education. It consists of 16 nationwide centers, which provide acute hospital and rehabilitation care. Inclusion criteria for the TBIMS database, from which numerous prospective and retrospective conditional studies have been derived, are as follows: moderate to severe TBI

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(posttraumatic amnesia [PTA] > 24 hours or LOC > 30 minutes or GCS in emergency department [ED] < 13 or intracranial neuroimaging abnormalities), admitted to ED within 72 hours of injury, age 16 years or greater at time of injury (NDSC, 2008).

Harrison-Felix et al. (2004) studied moderately to severely injured patients identified from the TBIMS database, which covered 15 TBI Model Systems Centers (TBIMSCs). Using vital-status information obtained from the Social Security Death Index, the authors found 161 deaths among 2,178 people with TBI followed for 17 days–12.8 years after injury for a mortality of 7.4%. Compared with age-sex-rate–specific mortality in the general population, the standardized mortality ratio (SMR) was 2.00 (95% CI, 1.69–2.31). The SMR for people with TBI who survived for more than 1 year after injury was only slightly lower, 1.95 (95% CI, 1.61–2.29). The median interval between injury and death was 2 years; of the 161 deaths, 38 occurred between rehabilitation discharge and 1 year after injury. Of the TBIs, 62% resulted from motor-vehicle crashes and 20% from acts of violence. The study participants had a mean age of 37 years; 76% were men, 60% were white, and 37% had severe TBI according to 24-hour postinjury GCS scores. Life expectancy was reduced by 5–9 years (average, 7 years), depending on age at injury, race, and sex.

Analysis of causes of death of the 124 people who survived more than 1 year after injury to a maximum followup of 13 years showed that 29% died from circulatory diseases, mainly ischemic heart disease (12%) or other heart disease (9%); 18% from external causes of injury and poisoning (5% from homicide, 7% unintentional, and 1% suicide); 14% from respiratory disease (7% pneumonia); 11% from infectious disease (9% septicemia); 9% from neoplasms (5% lung cancer); 7% from digestive diseases; and 4% in association with seizures (Harrison-Felix et al., 2006). People with TBI were at increased risk of dying from seizures (SMR, 37.17; 95% CI, 12.07–86.74), septicemia (SMR, 11.63; 95% CI, 5.58–21.38), pneumonia (SMR, 3.88; 95% CI, 1.68–7.65), unintentional injuries (SMR, 3.39; 95% CI, 1.81–5.80), or a digestive condition (SMR, 3.29; 95% CI, 1.42–6.49). The authors noted that the power of the study to detect specific outcomes was low.

Cifu et al. (1999) studied 665 enrolled patients (inclusion criteria differed in that patients presented to the ED within 24 hours after injury) in 1989–1996 in four geographically diverse TBIMSCs to assess incidence of rehospitalization. The rate of 1- and 2-year postinjury followup was 53% (351 of 665 and 281 of 534 eligible patients, respectively), and the 3-year followup rate was 47% (199 of 424 eligible patients). The rate of rehospitalization ranged from 20% to 22.5% over the 3-year period. Orthopedic or reconstructive surgery was the primary reason for rehospitalization (44%) during the first year; infections were also important, ranging from 8% to 17% during the 3-year period. After the first year, the rate of rehospitalization due to seizures and psychiatric issues increased from 6% to 15% 3 years after injury.

Marwitz et al. (2001) conducted a prospective study that assessed the cause and incidence of rehospitalization 1 and 5 years after head injury. A total of 1,547 patients admitted within 24 hours of injury from the 17 TBIMS in 1989–1999 were studied. Data indicated a rehospitalization rate of 23% (58% followup rate) at 1 year and a rate of 17% (55% followup rate) at 5 years. As seen in the work of Cifu et al. (1999), orthopedic or reconstructive surgery was the primary cause, 25%, at 1 year, decreasing to 13% at year 5. Rehospitalization due to infections went from 10% at 1 year to 8% at 5 years. In addition, rehospitalization related to seizures and psychiatric disorders ranged from 12% to 19%, increasing over the followup period.

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Nonelective rehospitalization accounted for 66% of admissions at 1 year, which increased to 83% at 5 years.

Brown et al. (2007) assessed physical impairment at time of rehabilitation admission and 1 year after injury. Patient data were drawn from the TBIMS database during 1988–2002. Mean GCS score of the sample (n = 3,463) was 10.6, mean duration of hospitalization was 51.5 days, and mean length of stay in the rehabilitation center was 30.3 days. Normal hearing (88%) and normal vision (82%) were common and did not differ between rehabilitation admission and 1 year. Normal swallowing improved from 61% to 95% of patients at 1 year. The percentage of patients with normal limb strength among the four limbs, ranged from 42% to 44% at admission, and increased to 82–84% at 1 year. Normal coordination and tone improved from the time of rehabilitation entry to 1 year (60.1–60.8% to 87.2–90.4% and 80.6–81.9% to 90.9–92.2%, respectively). Fewer than 19% of patients had normal standing balance and 48% normal sitting balance at admission; 1 year after injury, 76% had normal standing and 95% normal sitting balance.

Seel and colleagues (2003) evaluated the frequency of depression in a sample of 666 outpatients from the 17 TBIMSCs. Mean GCS score at the time of admission was 8.6 ± 4.6, mean PTA duration was 31.7 ± 26.2 days, and average evaluation time was 35.3 ± 26.9 months after injury. As specified in the DSM-IV, the Neurobehavioral Functioning Inventory was administered to identify symptoms of major depressive disorder. Of the participants, 27% reported problems in more than five of the nine criteria A symptoms and thus had a diagnosis of a DSM-IV major depressive disorder. The most commonly reported symptoms were fatigue (29%), distractibility (28%), anger or irritation (28%), and rumination (25%). A significant relationship was found between unemployment and low income status at the time of injury and postinjury depressive symptoms.

National Institutes of Health Traumatic Coma Databank

The Traumatic Coma Data Bank (TCDB) was a collaborative project between the National Institute of Neurological Disorders and Stroke and four clinical centers around the nation (the Medical College of Virginia at Richmond; the University of California, San Diego; the University of Virginia at Charlottesville; and the University of Texas Medical Branch at Galveston). All severely head-injured patients admitted to any of the centers from April 1983 to April 1988 were prospectively studied (Chesnut et al., 1993). Severe head injury was defined by a GCS of 8 or less at the time of or during the first 48 hours after admission and corresponded with lack of eye opening, lack of comprehensible speech, and the inability to obey commands (Levin et al., 1991b). A total of 1,030 patients were admitted to the four centers, with some variation in exclusion criteria, as described in the four studies below. Preinjury, hospital, and rehabilitation data on each participant were collected and analyzed; no external controls were included (Chesnut et al., 1993).

Levin et al. (1991b) investigated the outcome of vegetative states and consciousness after severe closed head injuries. A sample of 650 was obtained after several exclusions: 167 had gunshot wounds (16%), 121 were brain-dead on admission (14%), and 92 were younger than 16 years old (12%). Data were analyzed at the time of discharge and at followup of 6 months, 12 months, 2 years, and 3 years after injury. According to GCS scores and pupillary findings, the 93 patients (14% of the 650) who were discharged in a vegetative state had sustained more severe

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head injury than their conscious counterparts. Eighty-four patients were able to be followed up adequately, and the results are as follows: 40% became conscious by 6 months, 52% regained consciousness by 1 year, and 58% recovered consciousness within 3 years. Of the remaining 35 (42%) patients, 20 had died and 15 remained in their vegetative state. Analyses of neurologic and demographic features did not indicate any predictive factors for recovery.

Levin et al. (1991a) investigated the relationship between intracranial hypertension and memory deficit 6 months (n = 133) and 1 year (n = 126) after severe closed head injury, using neurobehavioral data from the TCDB. Memory was assessed by administering auditory verbal tests (prose recall from the Wechsler Memory Scale, the Selective Reminding Test, and the Digit Span subtest of the Wechsler Adult Intelligence Scale) and nonverbal visual tests. Those with intracranial hypertension in the first 72 hours after injury displayed some memory impairment at the 6-months assessment; impairment diminished with time and was not significant at the 1-year followup.

Chestnut et al. (1993) prospectively studied the effects of early and late hypotension (defined by systolic blood pressure≤ 90 mm Hg) on mortality in patients admitted to the TCDB. Of the 1,030 patients admitted, 284 were brain-dead, did not survive resuscitation, or had suffered gunshot wounds, and data on 47 were inadequate (with respect to prehospital course or initial blood pressure or arterial blood-gas results); therefore, 699 patients were eligible for study at the time of hospital arrival. Early shock, defined as hypotension from the time of injury to resuscitation, was experienced by 35% of patients. Mortality was associated with the occurrence of shock: no shock, 27%; shock any time during the early phase, 50%; and presenting with shock, 60%. The association between outcome and hypotension when age, hypoxia, and severe multiple trauma were controlled for was extremely significant ($p < 0.0001$). Late shock captured the remainder of the patients' stay after the first intensive-care-unit (ICU) shift (8 hours). Of the 493 eligible patients, 32% experienced late shock. There was a significant difference ($p < 0.001$) in mortality and morbidity between no shock (17%) and a recording of hypotension after the first ICU shift (66%).

Lu and colleagues (2005) retrospectively studied the decrease in mortality due to severe brain injury from 1984 to 1996. The sample consisted of extracted data from numerous study populations, including 635 patients from the TCDB in 1984–1987 (patients who had penetrating injury, who were deceased on arrival, or who were under 16 years old were excluded). The cohort also included 382 patients from the Medical College of Virginia and 822 from clinical-trial databases. In the total cohort of 1,839 patients, 526 (29%) died. Mortality in the severely brain-injured decreased from 39% in 1984 to 27% in 1996; there was a significant difference ($p < 0.0001$) in head-injury mortality between 1984–1987 (37%) and 1988–1996 (24%). After adjustment for a variety of factors—including age, admission motor score, and pupillary response—the difference remained significant ($p < 0.05$).

OTHER COHORT STUDIES

Bryant and Harvey Studies

Bryant and Harvey (1999a) conducted a prospective cohort study to compare rates of acute stress disorder (ASD) and PTSD in MVA survivors who sustained a mild TBI with rates in MVA survivors who did not have a TBI. A major trauma center in New South Wales, Australia,

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assessed admissions of adults who had been involved in an MVA over a 10-month period. Exclusion criteria for the cohort were inability to speak English, PTA for over 24 hours, not being medically fit or not being on narcotic analgesia other than codeine 4 weeks after trauma, and inability to be contacted. After application of exclusion criteria, 79 (55 male and 24 female) patients with mild TBI and 92 (61 male and 31 female) without mild TBI were evaluated 2–25 days after trauma. An assessment was administered 6 months after injury to 63 (80%) mild-TBI patients and 71 (77%) controls; 37 patients were lost to followup. The presence of ASD was assessed with the Acute Stress Disorder Interview (ASDI), and the presence of PTSD at 6 months was assessed with the PTSD module of the Composite International Diagnostic Interview (CIDI); both were administered by clinical psychologists. Mean injury severity score (ISS) was greater in mild-TBI patients (9.28) than in non–mild-TBI patients (4.0) ($p < 0.001$). Non-TBI patients reported fear and helplessness more often than mild-TBI patients during the acute and 6-month followup assessments; intrusive memories were also more common during the acute phase in non-TBI patients. There was no significant difference between 11 mild TBI and 12 non-TBI patients in the rates of diagnosed ASD (14% and 13%, respectively) or between 15 TBI and 18 non-TBI patients in rates of diagnosed PTSD (24% and 25%, respectively).

In a separate analysis of the same MVA population, Bryant and Harvey (1999b) investigated the relationship between PTSD and PCS in a population of mild-TBI patients. Over the period of study, 126 patients were initially identified; at the 6-month followup, 46 (32 male and 14 female) mild-TBI patients (mean ISS, 8.96; SD, 6.08) and 59 (31 male and 28 female) non-TBI patients (mean ISS, 3.92; SD, 3.74) were captured, representing 83% of the original sample. Assessments administered at 6 month were the PTSD module of the CIDI and the Postconcussive Symptom Checklist. Results indicated that 20% (n = 9) of mild-TBI patients and 25% (n = 15) of non-TBI patients met the criteria for PTSD diagnosis. Concentration deficits, dizziness, fatigue, headache, sensitivity to sound, and visual disturbances were reported more often by patients with PTSD than those without it in the mild-TBI sample; concentration deficits and irritability were reported more often in patients with PTSD than those without it in the non-TBI sample. Subjects with PTSD reported more frequent irritability than in those without PTSD in the mild-TBI sample.

With the same population as described above, Bryant and Harvey (1998) and Harvey and Bryant (2000) prospectively studied the frequency of ASD after mild TBI and its utility in predicting PTSD. Of 79 patients who sustained a mild TBI and were administered the ASDI within 1 month after trauma, 11 (14%) met the criteria for ASD. The CIDI module for PTSD was administered at 6 month (n = 63) and 2 years (n = 50) after injury; this represented a 63% retention rate of the original study group. At 6 month and 2 years after trauma, 24% (n = 15) and 22% (n = 11) of patients, respectively, met the criteria for PTSD. Of those with ASD, nine (82%) had a diagnosis of PTSD at 6 months and eight (80%) at the 2-year followup. Of those without ASD, six (12%) and three (8%) had PTSD at 6 months and 2 years, respectively.

University of Washington Longitudinal Traumatic Brain Injury Studies

A number of studies were based on a series of longitudinal investigations of health outcomes related to TBI conducted at the University of Washington by Dikmen and colleagues. The data from the studies have been formed into a repository and have been used to address questions about outcomes. The studies include Behavioral Outcome of Head Injury, Patient Characteristics and Head Injury Outcome, Dilantin Prophylaxis of Post-Traumatic Seizures, and

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Valproate Prophylaxis of Post-Traumatic Seizures. More information on the individual studies can be found in (Dacey et al., 1991; Dikmen et al., 1991, 2000; McLean et al., 1993; Temkin et al., 1990, 1999a, b). Participants in all the studies used in the present report were English-speaking adults who were admitted to the level I trauma center at Harborview Medical Center in Seattle, Washington, with head injuries and were followed for at least a year. Study subjects were consecutively admitted and met at least the following criteria: any period of LOC, PTA for at least an hour, or other objective evidence of head trauma; an injury that was serious enough to require hospitalization; and survival of at least a month after the injury, at which time the first assessment was done. The Behavioral Outcome of Head Injury and Dilantin Prophylaxis of Post-Traumatic Seizures studies both excluded people who had prior hospitalization for head injury, alcoholism, cerebral disease, a psychiatric disorder, or mental retardation. The Patient Characteristics and Head Injury Outcome study did not exclude subjects on the basis of those conditions. The Dilantin Prophylaxis of Post-Traumatic Seizures and the Valproate Prophylaxis of Post-Traumatic Seizures studies enrolled patients who had more severe head injuries that posed an increased risk of seizures, such as intracranial hematoma, cortical contusion, and depressed skull fracture. Studies to assess a variety of neurocognitive and social function outcomes have been conducted with these study populations.

Dikmen (1995b) conducted a prospective study of 436 adults with TBI recruited at the time of injury from a level 1 trauma center for the Behavioral Outcome of Head Injury, Patient Characteristics and Head Injury Outcome, or Dilantin Prophylaxis of Post-Traumatic Seizures study. The subjects made up 85% of the 514 subjects recruited into these studies. The controls were 132 patients enrolled as part of the Patient Characteristics and head Injury Outcome study who were admitted to the emergency room at Harborview Medical Center of University Hospital after trauma to any part of the body except the head; they were group-matched on age, sex, and education. Analyses weighted the cases to adjust the mix of severity and pre-existing conditions to approximate that of the unselected Patient Characteristics and Head Injury Outcome Study. A variety of neuropsychologic tests were conducted a year after injury. A year after injury, the TBI group performed significantly worse than controls on all the neurocognitive tests except the category test, on which the groups did not differ. A dose-response relationship between length of coma and level of performance on neurocognitive tests was observed at 1 year after injury; increasing degree of impairment was associated with increasing severity of brain injury. Subjects with the most severe TBI were significantly impaired on all neurocognitive measures.

Several other studies by Dikmen and colleagues used subsets of the same cohort of head-injured patients, but controls were friends of the head-injured patients (Dikmen et al., 1986, 1990) so they might not have controlled as well for general health effects of trauma. A study based on mild TBI found mild subtle neuropsychologic effects at 1 months that could no longer be detected at 1 year (Dikmen et al., 1986), whereas those with moderate to severe injuries demonstrated significant impairments at 1, 12, and 24 months after injury compared with healthy controls (Dikmen et al., 1990). Motor dexterity and speed were found to be sensitive to the effects of TBI even at 1 year after injury (Haaland et al., 1994). Memory functions were examined at 1 and 12 months after injury. At 1 year, only those with deep or prolonged impaired consciousness (represented by more than 1 day of coma, GCS score of 8 or lower, and PTA of 2 weeks or longer) were performing significantly worse than controls (Dikmen et al., 1987).

Dikmen et al. (1995c) examined 466 people who were enrolled as part of the Behavioral Outcome of Head Injury Study (21% of the subjects), the Patient Characteristics and Head Injury

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Outcome Study (50%), or the Dilantin Prophylaxis of Post-Traumatic Seizures Study, (29%). The controls were 124 trauma controls from the Patient Characteristics and Head Injury Outcome Study who had sustained bodily injury but not to the head and 88 healthy friends from the Behavioral Outcome of Head Injury Study. Analyses weighted the cases to adjust the mix of severity and pre-existing conditions to approximate that of the unselected Patient Characteristics and Head Injury Outcome Study. Social function was evaluated with the Glasgow Outcome Scale; a structured interview was conducted to collect information on independent living, school, employment, and income. The Sickness Impact Profile (SIP) was also administered. The head-injured were stratified by severity of injury. More severe TBI was related to worse outcome on all measures of social functioning except return to school, in which no difference was detected between TBI patients and trauma controls.

Return to work and other neurocognitive outcomes after head injury were assessed in subgroups of the same population (Dikmen et al., 1994; Doctor et al., 2005; Fraser et al., 1988; McLean et al., 1993). Fraser et al. (1988) found poorer neuropsychologic test scores and more dysfunction on the SIP physical scales at 1 month after injury in those who failed to return to work by 1 year after injury compared with those who had returned to work. McLean et al. (1993) assessed employment issues related to head trauma and found that in addition to a lower rate of return to work, participants with TBI were less likely to have remained at the same or similar position (36%) than the friend controls (60%). Dikmen et al. (1994) assessed time to return to work in 366 head-injured patients and 95 trauma controls who worked preinjury. The study participants were drawn from the three studies mentioned previously (45% from the Patient Characteristics and Head Injury Outcome Study, 33% from the Dilantin Prophylaxis of Post-Traumatic Seizures Study, and 22% from the Behavioral Outcome of Head Injury Study). Preinjury workers were followed for 1–2 years after injury to measure the time from injury to first return to work regardless of the length of the employment. Time to return to work was related to severity of TBI. Doctor et al. (2005) used a longitudinal inception cohort design and the same population as Dikmen et al. (1994) and additional TBI subjects from the Valproate Prophylaxis of Post-Traumatic Seizures Study. Employment was assessed at 1 year after injury in 418 TBI subjects who were working before their injuries and compared with expected unemployment rates from a current population survey. The authors found a substantial increase in risk of unemployment after TBI that increased with severity.

Several secondary studies have addressed other social outcomes. Patients with moderate to severe TBI were examined over a 2-year period. In spite of improvement, many subjects were unable to return to work, to support themselves financially, to live independently, or to participate in leisure activities for at least 2 years after injury (Dikmen et al., 1993). The authors examined alcohol use before and after injury and in relation to ED blood alcohol concentrations (Dikmen et al., 1995a); 42% of the subjects were intoxicated on arrival at the ED. The amount of drinking and associated problems decreased immediately after injury but were followed by an increase by 1 year although not to the same levels. Patients with more severe injuries decreased their drinking more than those with mild TBI. Blood alcohol in the ED was a good indicator of a history of problem drinking.

Burden to spouse and significant others was examined in the same cohort at 6 months after injury (Machamer et al., 2002). Significant others reported both favorable and unfavorable care-giving experiences. Adverse experience or burden was systematically related to increased

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TBI severity, worse cognitive outcome, increased dependence on others, reported change in the injured, and changes in the life of the significant other as a function of care-giving.

Dikmen et al. (2003) examined preinjury to postinjury changes in various facets of everyday life at 3-5 years after injury in subjects who had mild to moderate to severe TBI. Limitations were seen in all activities, including personal care, ambulation, travel, home management, and social relationships; the most affected were work, leisure and recreation, social relationships, and ambulation. The degree of limitations was related to the severity of TBI.

Machamer et al. (2005) used the same cohort to examine stability of work up to 3–5 years after injury. Amount of time worked after injury was related to severity of injury and associated impairments, in addition to preinjury work stability and earnings. Once a person returned to work, the ability to maintain uninterrupted employment was related to premorbid characteristics, such as being older, having higher income, and having had a preinjury job with benefits.

Pagulayan et al. (2006) used a subset of the same cohort as Dikmen et al. (2003) to examine recovery of function on the SIP at 1, 6, and 12 months and 3–5 years after injury. Significant limitations in all activities were seen at 1 month after injury compared with both friend controls and trauma controls. By 1 year, however, the TBI group still had problems compared with healthy friend controls but not with trauma controls except for leisure and recreation.

McLean and colleagues (1993) assessed psychosocial recovery at 1 and 12 months after head injury in 102 hospitalized patients (they were a subsample of (Dikmen et al., 1995c). The reference group included 102 friend controls matched for age, education, sex, and race. At 12 months after injury, the head-injured patients differed significantly in seven symptoms on the Head Injury Symptom Checklist: dizziness ($p < 0.01$), blurred vision ($p < 0.001$), concentration ($p < 0.001$), noise ($p < 0.05$), irritability ($p < 0.01$), temper ($p < 0.01$), and memory ($p < 0.001$). The median number of symptoms presented at 1 year was 5 in those with severe head injury, 2 in those with moderate head injury, 3 in those with mild head injury, and 2 in controls. The severely injured had significantly more symptoms than those with moderate injury or friend controls.

Jennett (Oxford, Rotterdam, Cardiff, and Manchester) Studies

Jennett and Lewin (1960) studied traumatic epilepsy in 1,000 patients (infants to 65 years old) who sustained nonmissile head injuries and were admitted to the Radcliffe Infirmary in Oxford from November 1948 to February 1952. The cohort consisted of the first 1,000 cases of the Roberts (1979) studies below. Criteria for admission included some period of unconsciousness; 58% of the patients had PTA lasting less than one hour and fewer than 20% over 24 hours, and fewer than 50% had a fractured skull (Jennett, 1975). Of the 1,000, 46 (5%) had no history of epilepsy but experienced early epilepsy within a week of admission (the 14 patients with a history of epilepsy were excluded). An unselected series of 821 patients were admitted directly from the accident site and immediately placed under care; 31 (4%) experienced early epilepsy within a week of admission. A selected series of 179 patients were transferred from other hospitals and in general were considered more severe and complicated; 15 (8%) experienced early epilepsy. Of the total population, 90 patients died, including eight (9%) who had early epilepsy. Of the 75 children under 5 years old and the 122 who were 6–15 years old, 9% and 3%, respectively, had early epilepsy. Early epilepsy was more frequent in patients who experienced PTA for over 24 hours. On followup after 4 years, late epilepsy was present in 28

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(10%) of 275 patients. The latter population included all who experienced early epilepsy and 100 randomly selected patients with uncomplicated injures and PTA of less than 24 hours. Of those with early epilepsy, 29% experienced late epilepsy—an incidence 4 times higher compared to those without (Jennett and Lewin, 1960).

Jennett (1969) expanded the Oxford series to include a total of 189 patients with epilepsy (within 8 weeks of injury); 150 cases of epilepsy within the same period were also added and known as the Glasgow series. Results were consistent with previous studies: an increased risk of late epilepsy was found in people with nonmissile injuries who had early epilepsy. Early epilepsy (within 1 week of injury) occurred 30 times more often than in the following 7 weeks (Jennett, 1969, 1973). A group of 73 patients with missile injuries was included for comparison; results indicated that early epilepsy is not necessarily predictive of late epilepsy in such patients, inasmuch as the baseline risk of late epilepsy is already high; 45% of those with missile injuries develop late epilepsy (Jennett, 1969, 1973).

Jennett (1962) examined early and late epilepsy by studying 381 patients who sustained blunt head injuries: 139 had early epilepsy, 282 late epilepsy, and 40 both early and late epilepsy. The population was drawn from the 46 patients with early epilepsy in the Oxford series, 93 patients with early epilepsy in Manchester and Cardiff, UK, and patients at the Oxford Infirmary outside the study dates. The late-epilepsy series consisted of 58 followup patients with late epilepsy (drawn from 75 patients with early epilepsy and 240 without early epilepsy in the 1,000-patient Oxford series) and 224 patients who presented with a history of head injury and epilepsy. Results were consistent with previous and later studies of this cohort in that a relationship was found between more severe injury (longer PTA, depressed fracture, and early epilepsy) and development of late epilepsy.

The effect of depressed fractures on the incidence of epilepsy was studied in over 600 patients from both the Oxford and Glasgow series—333 patients were followed for over 1 year after injury, and 219 were followed for more than 4 years. Early epilepsy was seen in 10% of those with depressed fractures and 4% of those without; late epilepsy was seen in 21% of those with depressed fractures and 8% of those without (Jennett, 1969).

Jennett (1973) studied patients from the original Oxford series, patients from the Glasgow series, and 250 patients with depressed fractures from Rotterdam to investigate known risk factors for late epilepsy: early epilepsy, intracranial hematoma (evacuation within 14 days of injury), and depressed fracture. The results supported those of previous studies. In addition, 75% of patients who had one late epileptic episode experienced seizures over the following 2 years, and over 33% experienced at least one seizure per month.

Jennett (1975) summarized previous findings on nonmissile injuries from the combined Oxford, Glasgow, and Rotterdam series.

Roberts (Oxford, UK) Studies

Roberts (1979) examined the relationship between a single nonmissile head injury and characteristics of mental and physical disability 3–25 years after injury in two groups of patients. The study population consisted of 548 patients (11 eventually lost to followup) from a total population of 7,000 patients admitted after accidental head injury to the Accident and Neurosurgical Services of the Radcliffe Infirmary, Oxford, England, in 1948–1961. The study population included patients 5–83 years old who remained unconscious or amnestic for a week

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or longer. Those who developed intracranial infection or sustained spinal-cord or brachial plexus lesion in addition to head injury, American ex-service personnel for whom there was no adequate method of followup, and foreign nationals isolated from their native culture were excluded. Eighty percent of patients were admitted within hours and directly from the accident scene, and 20% were transfers from facilities that lacked adequate neurosurgical treatment. A consecutive series consisted of 479 patients, and a selected series consisted of 69 patients who had presented at the Addenbrooke Hospital in Cambridge in 1948–1970. The latter group consisted of severely head-injured patients who had remained unconscious for 1 month or longer after injury. Eleven patients were lost to followup, and 206 were no longer alive; that left 331 surviving patients (291 from the consecutive series and 40 from the selected series), who were invited for interview and re-examination at the Addenbrooke Hospital or the Radcliffe Infirmary. Close relatives, spouses, or parents were interviewed for 82% of the patients in the consecutive series and 93% of the patients in the selected series. Forty-two patients declined to attend and were visited in their homes. Six survivors were not examined by the authors, but were seen by another neurologist. Intellectual, personality, and neural deficits in each patient were assessed through interview; patients were then administered a neurologic examination while relatives, if available, were questioned by a psychiatric social worker with regard to past and present behavioral issues. Most were assessed by neuropsychologists who tested memory and intellectual deficits. Intellectual function and memory tests (including verbal memory functions) and tests of visuospatial function were administered by a clinical psychologist to assess cognitive deficits. All patients underwent neurologic examination, and 217 were given a series of cognitive-function tests.

Roberts (1979) also assessed patients for disordered hypothalamic and pituitary function. Results indicated that anterior hypopituitarism did not increase in frequency because of head trauma; at the time of the study, only one patient had that diagnosis (a 10-year-old boy). The incidence of diabetes insipidus (diagnosed on the basis of polyuria) in the consecutive series was eight of 291 patients (3%). Hypothalamic hyperphagia was diagnosed in 16 of 291 (5%) in the consecutive series and six of 40 (15%) in the selected series. Lower age and greater severity of injury seem to contribute to increased rates of diabetes insipidus and hyperphagia among the injured.

Positional vertigo was identified in 71 (24%) of the consecutive-series patients 10 years after injury; 58 (20%) reported persistent headaches (all four types, as classified by severity) several years after injury. No clear association was found between symptoms and age, complications, or severity of injury. Incidences, however, are likely to be underestimates, inasmuch as vertigo and headache are underreported in cases of severe head injury (Roberts, 1979).

Posttraumatic epilepsy was assessed 10–24 years after injury in the consecutive series: 75 (26%) had one or more seizures during the study period; 22 (29%) of those were early (within 1 week after injury). The results were consistent with those of the Jennett studies described above (Roberts, 1979).

Lewin et al. (1979) determined the causes of death of 75 severely injured patients who had been discharged from the Radcliffe Infirmary 10–24 years earlier with severe TBI (the patients had remained unconscious for a week or more). No rates of death were given. Compared with the general population of England and Wales, deaths from meningitis (SMR, 65), epilepsy (SMR, 40), drowning (SMR, 20), and respiratory diseases (SMR, 2) were increased. No excesses of deaths from suicide, accidents, cardiovascular or cerebrovascular disease, or malignancies

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were observed. In addition, the overall prevalence of posttraumatic epilepsy was 28% in the consecutive series and ranged from 7% in those with uncomplicated injury and PTA of less than a week to 61% in those with complicated injury (compression and traumatic or surgical penetration). An increase in the prevalence of seizures was seen with length of PTA (uncomplicated) and with duration of coma (complicated and uncomplicated).

STUDIES OF SPORTS-RELATED TRAUMATIC BRAIN INJURY

Concussions are relatively common in people who participate in contact sports, so studies of such people afford a unique opportunity to assess the short-term and long-term consequences of head injury. It is estimated that over 300,000 sports-related concussions occur each year in the United States (Guskiewicz et al., 2005). The studies discussed below focus on the long-term health outcomes related to sports-related TBI. Although not all the studies include large cohorts, the committee believed that it was important to discuss the strengths and limitations of studies of sports-related TBI. Contact sports provide a useful laboratory for assessing the influence of recurring mild TBI on such health outcomes as dementia and Alzheimer disease. One advantage of studies of sports-related TBI is that there is a large population to draw from. A major limitation, however, is that many studies are based on self-reported measures. For instance, participants' TBIs are commonly ascertained by asking subjects whether they recall having had a concussion or, less commonly, whether they had a clinical diagnosis of a head injury.

Football

American football is a "collision sport" that is widely known for causing a variety of injuries, including cerebral concussions. It has been reported that a large percentage of professional football players have sustained at least one concussion during their careers (Guskiewicz et al., 2005).

Guskiewicz and colleagues (2005, 2007) studied the association of recurrent concussions sustained and long-term health outcomes, including mild cognitive impairment and risk of depression in retired professional football players. The authors originally sent a survey to all 3,683 living members of the National Football League Retired Players Association. The survey instrument included questions about musculoskeletal, cardiovascular, and neurologic conditions experienced during and after the football career. Questions were also asked about the number of concussions sustained during the football career and the presence of such health conditions as depression, Parkinson disease, Alzheimer disease, and schizophrenia (Guskiewicz et al., 2005). Concussion history was based on players' recall of injury events, and *concussion* was defined as "injury resulting from a blow to the head that caused an alteration in mental status and one or more of the following symptoms: headache, nausea, vomiting, dizziness/balance problems, fatigue, trouble sleeping, drowsiness, sensitivity to light or noise, blurred vision, difficulty remembering, and difficulty concentrating". The mailed questionnaire included the SF-36 Measurement Model for Functional Assessment of Health and Well-Being to assess daily-living functioning. A physical-health composite score was calculated. The authors sent out a second questionnaire to a subset of 1,754 of the original population that included questions on memory and issues related to mild cognitive impairment.

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Results were cross-tabulated from the initial questionnaire. Of the original 3,683 general health surveys distributed, 2,552 (69%) were completed. Of those who responded, 1,513 (61%) reported having sustained at least one concussion, and 597 (24%) reported three or more concussions. The authors found an association between recurrent concussion and clinically diagnosed mild cognitive impairment (MCI) ($p = 0.02$) and self-reported significant memory impairment ($p = 0.001$). People who reported sustaining three or more concussions had a 5-fold prevalence of MCI diagnosis and a 3-fold prevalence of reported significant memory problems compared with those without a history of concussion. The authors found no association between recurrent concussion and Alzheimer disease but observed earlier onset of Alzheimer disease in the retired football players than in the general American male population.

Guskiewicz and colleagues (2007) restudied the same population of 2,552 retired football players to investigate the association between prior head injury and diagnosis of clinical depression. They found that 269 (11%) of the respondents reported a prior or current diagnosis of clinical depression and found an association between recurrent concussion and diagnosis of lifetime depression ($p < 0.005$). Retired players reporting three or more concussions were 3 times more likely to have a diagnosis of depression than players with no history of concussion. Similarly, those with a history of one or two previous concussions were 1.5 times more likely to have a diagnosis of depression than players with no history of concussion.

As mentioned previously, an important limitation of these studies is that they rely on self-reports of exposure (TBI). Because history of head injury is based on recollection of events that occurred many years before the survey, substantial recall bias may be introduced.

Boxing

Sports literature has been used to evaluate boxers and to assess the effects of repetitive head injury on long-term health outcomes, particularly neurologic and neurocognitive outcomes, such as dementia pugilistica and the relationship between the APOE e4 gene and chronic TBI. A number of the studies discussed below assess long-term health outcomes in brain-injured boxers, including two (Porter, 2003; Porter and Fricker, 1996) that study the same cohort of boxers.

Porter and Fricker (1996) conducted a neuropsychologic assessment of 20 amateur boxers 16–25 years old in the six largest boxing clubs in Dublin, Ireland, and 20 controls matched for age and socioeconomic status. Each amateur boxer was to have competed in a minimum of 40 amateur matches. The boxers and the controls were given a battery of neuropsychologic tests by an independent examiner initially in 1992 and then again 15–18 months later. The tests included Trail-Making Tests A and B, Finger Tapping Tests (FTT), and the Paired Associate Learning test. The authors found that the boxers performed significantly better then the controls in Trail-Making Tests A and B. However, the control group's scores on the FTT were significantly higher than those of the boxers. The authors noted that there was no evidence of neuropsychologic impairment in the boxers compared with the controls, and they found no association between boxing and performance on any of the neuropsychologic tests.

Porter (2003) conducted a followup study of the same population of 20 amateur boxers and 20 matched controls. Again, the subjects underwent a battery of neuropsychologic tests after an initial assessment at 18 months, 4 years, 7 years, and 9 years. The boxers scored higher than the controls on Trail Making Tests A and B at all times and lower on the FTT at all times except baseline for the dominant hand. The authors found no evidence of neuropsychologic impairment

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over the 9-year period; in fact, the boxers improved on some of the tests in comparison with the controls.

Soccer

Studies of soccer players have been conducted to evaluate the association of TBI with long-term health outcomes, particularly neurocognitive outcomes. Soccer is a popular sport that is considered relatively safe for the general population; however, it is designated a contact sport because rates of concussion in soccer players are high and have been found to be equivalent to those in football players (Matser et al., 1998).

Matser et al. (1998), Guskiewicz et al. (2002), Rutherford et al. (2005), and Straume-Naesheim et al. (2005) conducted studies of neurocognitive outcomes related to soccer-related head injuries. Two studies found neuropsychologic impairment in head-injured soccer players. Matser and colleagues (1998) assessed neurocognitive impairment in soccer players with chronic TBI and found that soccer players performed worse than controls on neurocognitive tests of planning, memory, and visuoperceptual tasks. The number of concussions was inversely related to scores on neurocognitive tests. Rutherford and colleagues (2005) studied neuropsychologic impairment in amateur soccer, rugby, and non-contact–sports players and found that the number of head injuries was a significant predictor of scores on the Trails B response test ($p = 0.014$) and the Test of Attention Performance Divided Attention ($p = 0.020$). The latter study was designed to be exploratory.

Two other studies, however, did not find a relationship between soccer-related TBI and neurocognitive outcomes. Guskiewicz and colleagues (2002) evaluated neurocognitive outcomes in collegiate athletes (including participants in soccer and other sports) and found no significant relationship between a history of soccer-related concussions and scholastic aptitude or neurocognitive performance. Straume-Naesheim and colleagues (2005) studied neuropsychologic impairment in head-injured Norwegian elite soccer players; lifetime heading exposure was not associated with neuropsychologic test performance.

As with much of the sports literature discussed above, diagnosis of TBI in studies of soccer players was generally based on self-reports of exposure (for example, questionnaires that asked about number of concussions in the past or number of headings in previous matches) or on surrogates of exposure (such as number of games played). Reliance on self-reports of exposure may introduce recall bias, and this should be considered in evaluating the results of the studies.

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TABLE 5.1 Major Cohort Studies (Shaded) and Derivative Studies

Reference	Eligible Population	Type of Study or Methods	Date(s) of Enrollment	Subgroup (n = Eligible Subjects)	Contacted or Located (% of Eligible)	Responded or Enrolled (Response Rate)	Comments
Walker's Studies of Head-Injured Bavarian World War I Veterans							
Walker et al., 1971	1,000 Bavarian men with head injuries from World War I randomly selected from among 5,500 cases at head-injury center 1916–1927 with "sufficient information for analysis" of nature of injury; 1,000 unwounded Bavarian World War I veterans on pension lists for receiving medal; all born 1880–1900.	Cohort	1916–1927	1,000 men randomly selected from among 5,500 cases at head-injury center in 1916–1927 with "sufficient information for analysis" of nature of injury 1,000 unwounded Bavarian World War I veterans on pension lists for receiving medal	555 cases, 563 controls	555 cases, 563 controls	

Reference	Purpose	Study Design	Population (where appropriate)			Comments
			Eligible	Located	Enrolled (Response Rate)	
Weiss et al., 1982	Mortality	Cohort	1,010 Bavarian men with head injuries from World War I; 1,000 unwounded Bavarian World War I veterans; final numbers: 647 cases, 616 controls			

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Reference	Eligible population	Type of study or methods	Date(s) of enrollment	Subgroup (n=eligible subjects)	Contacted or located (% of eligible)	Responded or enrolled (Response rate)	Comments
Walker's Studies of Head-Injured World War II Veterans							
Walker and Erculei, 1969	Head-injured men wounded in World War II who were studied at Cushing General Hospital in Framingham, MA, in 1945–1946 (experienced at least one posttraumatic epileptic seizure) or were identified through Army and VA pension rosters as part of followup in Baltimore in 1950–1954 (unselected) Baltimore group was matched in class and severity of injury	Cohort	Group 1 (Cushing General Hospital, Framingham, MA): enrolled 1945–1946 (n = 241) Group 2 (Baltimore group): enrolled 1950–1954 (n = 123)	364	Of 364 men originally identified, information obtained on 343 (94%)	313 (of 343 men, 21 refused to participate, 30 died)	No external comparison—all comparisons between those with and without posttraumatic seizures

Reference	Purpose	Study design	Population (where appropriate) Eligible	Located	Enrolled (Response rate)	Comments
Walker and Erculei, 1969	Posttraumatic symptoms, including nervousness, headache, irritability, easy fatigability, impaired memory, dizziness, impaired mentation, lack of concentration, insomnia, intolerance to alcohol	Cohort	313 men examined, questioned for relevant symptoms			
Walker and Erculei, 1969	Neurologic deficit	Cohort	Neurologic deficit assessed with two subgroups of population: patients with no neurologic deficit (n = 50), patients with neurologic deficit (n = 199)			
Walker and Erculei, 1969	Socioeconomic status, employment status	Cohort	Cohort divided into two groups: employed (n = 182), unemployed (n = 121)			

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Reference	Purpose	Study design	Population (where appropriate) Eligible	Located	Enrolled (Response rate)	Comments
Walker and Erculei, 1969	Posttraumatic epilepsy	Cohort	Comparison of subset of Group 1 (Cushing General Hospital), which included 232 men with posttraumatic epilepsy, and Group 2 (Baltimore group), which included 123 men with posttraumatic encephalopathy.			
Walker and Erculei, 1970	Posttraumatic epilepsy	Cohort	Comparison of subset of Group 1 (Cushing General Hospital), which included 230 men with posttraumatic epilepsy, and Group 2 (Baltimore group), which included 123 men with posttraumatic encephalopathy.			

Reference	Eligible population	Type of study or methods	Date(s) of enrollment	Subgroup (n=eligible subjects)	Contacted or located (% of eligible)	Responded or enrolled (Response rate)	Comments
Finnish Studies							
Achte et al., 1969	Veterans who suffered mild, moderate, or severe open and closed head injuries in Finnish wars of 1939–1945; 3,552 men with mild, moderate, or severe open and closed head injuries were studied 22–26 years after injury	Prospective cohort	1939–1945				

Reference	Purpose	Study design	Population (where appropriate) Eligible	Located	Enrolled (Response rate)	Comments
Achte et al., 1991	Psychiatric disturbances	Prospective cohort	In more inclusive sample, 10,000 men with mild, moderate, or severe open, closed head injuries were studied 50 years after injury			No comparison group

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Reference	Eligible population	Type of study or methods	Date(s) of enrollment	Subgroup (n=eligible subjects)	Contacted or located (% of eligible)	Responded or enrolled (Response rate)	Comments
Teuber's Cohort							
Weinstein, 1954	World War II (and to smaller extent World War I and Korean War) veterans who sustained penetrating brain injuries or peripheral nerve injuries	Case–control study	1948–1950s	Over 300			

Reference	Purpose	Study design	Population (where appropriate) Eligible	Located	Enrolled (Response rate)	Comments
Teuber and Weinstein, 1954	Spatial and motor function	Case–control	35 veterans with penetrating brain injuries, 12 veterans with peripheral nerve injuries from the original series			
Weinstein and Teuber, 1957a	Intelligence scores	Case–control	62 veterans with penetrating brain injuries, 50 veterans with peripheral nerve injuries for whom preinjury Army General Classification Test score was available			
Weinstein and Teuber, 1957b	Intelligence scores	Case–control	62 veterans with penetrating brain injuries, 50 veterans with peripheral nerve injuries for whom preinjury Army General Classification Test score was available			
Weinstein et al., 1958	Sensorimotor discrimination	Case–control	40 World War II, 3 Korean War veterans with penetrating head injuries, 20 controls with peripheral nerve injuries from original series			
Corkin et al., 1984	Life expectancy	Case–control	190 World War II veterans with penetrating head injuries, 106 World War II veterans with peripheral nerve injuries who were in original series			
Corkin et al., 1989	Cognitive performance	Case–control	57 men with penetrating head injuries, 27 with peripheral nerve injuries who were in original series			

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Reference	Eligible population	Type of study or methods	Date(s) of enrollment	Subgroup (n=eligible subjects)	Contacted or located (% of eligible)	Responded or enrolled (Response rate)	Comments
W.F. Caveness Studies of Korean War Veterans							
Caveness, 1963	Military personnel of Korean War who suffered head injuries and were treated in either US Naval Hospital in Yokusaka or US Navy hospital ships off coast of Korea	Prospective cohort				467	No reference group.

Reference	Purpose	Study design	Population (where appropriate) Eligible	Located	Enrolled (Response rate)	Comments
Evans, 1962	Posttraumatic epilepsy	Cohort	422 Korean War veterans with head injuries treated in US Naval Hospital in Yokusaka or in US hospital ships, assessed 3–11 years after injury 422 men who had sustained head injury during Korean War; of original 493 in cohort, 33 were excluded because they were not in US armed forces at time of injury, 10 because of inadequate information on original head injury, 12 because injuries were related to face or cervical spine, 2 because seizures were responsible for initial head injury, 1 because head injury was probably early effect of chronic encephalitis, 12 because they died during period, 1 because admission to hospital was determined by first epileptic seizure after previous head injury			No reference group; no screening for preinjury seizure disorder
Caveness et al., 1962	Posttraumatic epilepsy	5 retrospective cohorts from 3 wars (World War I, World War II, Korean War)	407 Korean War veterans with head injuries (214 missile, 52 blast, 141 blunt), 135 with dura mater rupture, assessed 5 years after trauma			No reference group; undetermined whether preinjury seizures
Caveness, 1963	Posttraumatic epilepsy	Cohort	356 Korean War veterans with head injuries assessed 8–11 years after injury			No reference group; no screening for preinjury seizure disorder
Caveness, 1966	Neurologic deficits	Cohort	356 Korean War veterans with head injuries assessed 8–11 years after injury			No reference group

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Reference	Eligible population	Type of study or methods	Date(s) of enrollment	Subgroup (n=eligible subjects)	Contacted or located (% of eligible)	Responded or enrolled (Response rate)	Comments
Vietnam Head Injury Study							
Caveness, 1972	Phase I: Head-injured Vietnam soldiers who survived first week after sustaining head injury	Registry; medical-records review	1967–1970	1,539			
Phase II – National Naval Medical Center, 2008	Phase II: Head-injured subjects from original registry and 85 matched normal volunteers evaluated in 1981–1984, 12–15 years after injury	Retrospective cohort	1981–1984		520	520	
Grafman, 2007	Phase III: 182 of 520 head-injured subjects who were assessed in phase II were included in phase III; 17 patients identified in phase I who did not attend phase II were assessed; 32 of original 85 control subjects in phase II attended phase III; 23 were newly recruited for phase III	Retrospective cohort	2004–2006	520	484 (93%)	182 from phase II (38%), 7 new enrollees	

Reference	Purpose	Study design	Population (where appropriate)			Comments
			Eligible	Located	Enrolled (Response rate)	
Weiss et al., 1983	Posttraumatic epilepsy	Retrospective cohort	Participants from phase I, including 378 of 1,221 participants found to have posttraumatic seizures			
Rish et al., 1983	Mortality, posttraumatic epilepsy	Prospective cohort	Participants from phase I, including 1,127 male Vietnam veterans alive 1 week after trauma			

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Reference	Purpose	Study design	Population (where appropriate)			Comments
			Eligible	Located	Enrolled (Response rate)	
Salazar et al., 1985	Posttraumatic epilepsy	Retrospective cohort	Participants from phase I, including 421 (of 1,131) head-injured men			No reference group; unclear whether had preinjury seizures
Grafman et al., 1986	Face discrimination, memory	Retrospective cohort	Participants from phase II, including 213 men with penetrating TBI, 49 controls			Assessed outcomes based on region of brain affected
Salazar et al., 1986	Intelligence, reasoning, attention; memory, verbal free recall, nonverbal memory, language	Retrospective cohort	Participants from phase II including 15 veterans who suffered unilateral penetrating missile wounds to basal forebrain, 49 uninjured controls, 113 patients with lesions elsewhere in brain			Assessed outcomes based on region of brain affected
Kraft et al., 1993	Occupational, educational achievement	Retrospective cohort	Participants from phase II, including 520 men with penetrating head injury, 85 uninjured controls			
Schwab et al., 1993	Measured work status 15 years after injury; neurologic, neurophysiologic, social-interaction impairments	Retrospective cohort	Participants from phase II, including 520 men with penetrating head injury, 85 uninjured controls			Assessed work outcomes
Grafman et al., 1996	Violence, aggression	Retrospective cohort	Participants from phase II, including 279 male veterans, 57 healthy controls			Assessed outcomes based on region of brain affected
Groswasser et al., 2002	Cognitive, vocational outcome	Retrospective cohort	Participants from phase II, including 74 with penetrating head injury, 37 with closed head injury			
Koenigs et al., 2007	PTSD	Retrospective cohort	Participants from phase III, including 193 veterans with lesions distributed throughout brain (as result of penetrating head injuries sustained during combat), 52 veterans with combat exposure but no brain injury			
Raymont et al., 2008	Cognitive outcomes	Retrospective cohort	Participants from phase III, including 520 with head injury from original registry, 85 matched healthy volunteers, evaluated in 1981–1984, 12–15 years after injury; of 520 from phase II, 484 still alive, 182 attended phase III.			

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Reference	Eligible population	Type of study or methods	Date(s) of enrollment	Subgroup (n=eligible subjects)	Contacted or located (% of eligible)	Responded or enrolled (Response rate)	Comments
Vietnam Experience Study							
Luis et al., 2003	Male US Army veterans who entered military and served at least 4 mo on active duty: 9,324 who served single tour in Vietnam, 8,989 who served elsewhere		January 1965–December 1971	4,462 veterans randomly selected from eligible population			

Reference	Purpose	Study design	Population (where appropriate)			Comments
			Eligible	Located	Enrolled (Response rate)	
Luis et al., 2003	PPCSC	Cross-sectional cohort sample	3,957 veterans of original population; 329 excluded because they did not meet criteria for either ICD-10 or DSM-IV PPCSC, but not both; 55 excluded because of hospitalization; 121 excluded because of incomplete data			
Vanderploeg et al., 2007	Psychiatric, neurologic, psychosocial outcomes	Cross-sectional cohort sample	4,384 veterans of original population; 40 excluded because of hospitalization after injury; 38 excluded because of incomplete data			
Vanderploeg et al., 2003	Work, marital status	Logistical regression analysis	4,322 veterans of original population; 53 excluded because of hospitalization after injury; 87 excluded because of incomplete data			
Vanderploeg et al., 2005	Neuropsychologic outcomes	Cross-sectional cohort sample	4,384 veterans of original population; 40 excluded because of hospitalization after injury; 38 excluded because of incomplete data			

Reference	Eligible population	Type of study or methods	Date(s) of enrollment	Subgroup (n=eligible subjects)	Contacted or located (% of eligible)	Responded or enrolled (Response rate)	Comments
Rochester Epidemiology Project							
Melton, 1996	Residents of Rochester, Olmsted County, MN	Medical-records linkage system	1910–present	Population of Olmsted County, MN			

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Reference	Purpose	Study design	Population (where appropriate)			Comments
			Eligible	Located	Enrolled (Response rate)	
Annegers et al., 1979	Cancer	Double cohort	All traumatic brain injuries in Olmstead County, MN, 1935–1974; patients must have survived initial trauma and had no known pre-existing tumor; 2,953 patients followed for total of 29,859 person-years			
Annegers et al., 1980	Seizures	Population-based retrospective cohort	2,747 patients of Olmstead County, MN, with head injuries sustained 1935–1974			
Chandra et al., 1989	Alzheimer disease	Population-based retrospective cohort	All incident cases of clinically diagnosed Alzheimer disease in population of Rochester, MN, with onset 1965–1974 (n = 274)			
Williams et al., 1991	Dementia, parkinsonism, ALS, PD	Population-based retrospective cohort	821 Olmsted County residents with head trauma and presumed brain injury occurring 1935–1974			
Siva et al., 1993	Multiple sclerosis	Population-based retrospective cohort	225 incident cases of multiple sclerosis 1905–1991, 164 prevalence cases (December 1, 1991) of definite MS in population of Olmsted County, MN			
Kurland, 1994	Multiple sclerosis	Population-based retrospective cohort	All cases of MS diagnosed in Olmsted County, MN, 1905–1991 (n = 223)			
Annegers et al., 1995	Seizures	Population-based retrospective cohort	Incidence of acute symptomatic seizures in population of Rochester, MN, 1935–1984 (696 episodes of incident acute symptomatic seizures in 692 people; 4 people had two episodes with different etiologies)			
Annegers et al., 1998	Seizures	Population-based retrospective cohort	4,541 patients residing in Olmstead County, MN, with head injuries sustained 1935–1984			
Nemetz et al., 1999	Alzheimer disease	Population-based retrospective cohort	Cohort consisted of all Alzheimer disease incident cases diagnosed in 1965–1984 in Olmstead County, MN; 151 cases excluded because previously identified as having history of head trauma			
Singer, 2001	Seizures	Population-based retrospective cohort	4,541 patients residing in Olmstead County, MN, with head injuries sustained 1935–1984			
Bower et al., 2003	Parkinson disease	Case–control study	196 Parkinson disease patients living in Olmstead County, MN, with onset 1976–1995			
Brown et al., 2004	Mortality after TBI	Population-based retrospective cohort	Any Olmstead County, MN, resident with medically attended TBI in 1985–1999 (n = 45,831); random 15.7% sample of TBI patients (n = 7,175) reviewed, 1,448 met inclusion criteria			
Flaada et al., 2007	Mortality after TBI	Population-based retrospective cohort	17% of all TBI patients in (total = 45,791) Rochester Epidemiology Project, 1985–1999; sample = 7,800; 1,443 met TBI case definition			

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Reference	Eligible population	Type of study or methods	Date(s) of enrollment	Subgroup (n=eligible subjects)	Contacted or located (% of eligible)	Responded or enrolled (Response rate)	Comments
Community-Based Study of Injuries in the Aquitaine, France							
Tiret et al., 1989	People living in Aquitaine, France, who sustained injury in 1985–1986	Population	December 1985–December 1986	2.7 million (1986 population in region)	During 1-year period, 1,181 deaths registered from death certificates, 8,190 hospital admissions observed during sampling periods in residents of Aquitaine		

Reference	Purpose	Study design	Population (where appropriate)			Comments
			Eligible	Located	Enrolled (Response rate)	
Masson et al., 1996	Self-reported functional status	Prospective cohort	231 head-injured with various degrees of head injury; 80 controls with lower-limb injury (LLI); 64 LLI, 176 head injured patients reviewed (114 minor, 35 moderate, 27 severe)			
Masson et al., 1997	Disability	Prospective cohort	407 head-trauma patients; 5 years after injury, 64 patients deceased, 36 lost to followup			

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Reference	Eligible population	Type of study or methods	Date(s) of enrollment	Subgroup (n=eligible subjects)	Contacted or located (% of eligible)	Responded or enrolled (Response rate)	Comments
Canadian Study of Health and Aging							
CSHA, 2008	Representative sample of Canadian population 65 years old or older on October 31, 1990, in 39 urban centers, rural areas in 10 Canadian provinces	Population-based cohort	1991–2002			CSHA-1: 9,008; CSHA-2: 5,703 CSHA-3: 3,437	

Reference	Purpose	Study design	Population (where appropriate) Eligible	Located	Enrolled (Response rate)	Comments
CSHA, 1994	Alzheimer disease, CSHA-1	Prospective population-based cohort	258 with Alzheimer disease			
Lindsay et al., 2002	Alzheimer disease, CSHA-2	Prospective population-based cohort	194 with Alzheimer disease, 3,894 controls			

Reference	Eligible population	Type of study or methods	Date(s) of enrollment	Subgroup (n=eligible subjects)	Contacted or located (% of eligible)	Responded or enrolled (Response rate)	Comments
Traumatic Brain Injury Model Systems							
NDSC, 2008	Patients entered into any nationwide Traumatic Brain Injury Model Systems Centers and meeting the following criteria: moderate to severe TBI (PTA >24 h or LOC >30 min or GCS in ED <13 or intracranial neuroimaging abnor-malities); admitted to ED within 72 h of injury; >16 years old at time of injury	Prospective, longitudinal multicenter	1987– present				

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Reference	Purpose	Study design	Population (where appropriate)			Comments
			Eligible	Located	Enrolled (Response rate)	
Harrison-Felix et al., 2004	Mortality	Retrospective	2,178 patients in 15 TBI Model Systems Centers treated 1988–December 31, 2000			
Harrison-Felix et al., 2006	Mortality	Retrospective	2,140 people surviving 1 year after injury in 15 TBI Model Systems Centers treated 1988–December 31, 2000			
Cifu et al., 1999	Rehospitalization	Prospective	665 patients admitted to ED within 24 h of injury to four TBI Model Systems Centers 1989–1996; response rate for both 1 and 2 years after injury 53% of eligible patients, 3-year response rate 47%			
Marwitz et al., 2001	Rehospitalization	Prospective	1,547 patients admitted within 24 h of injury to 17 TBI Model Systems Centers 1989–1999; 1-year followup 895 (58%) patients; 5-year followup 442 (55%) patients			
Brown et al., 2007	Physical impairment	Prospective longitudinal multicenter descriptive analysis	3,463 people in TBI Model Systems database 1988–2002 with complete physical examination data at rehabilitation admission, 1 year after injury			
Seel et al., 2003	Depression	Prospective	666 patients derived from 17 TBI Model Systems Centers who received followup evaluations 1996–2000 (10–26 mo after injury)			

Reference	Eligible population	Type of study or methods	Date(s) of enrollment	Subgroup (n=eligible subjects)	Contacted or located (% of eligible)	Responded or enrolled (Response rate)	Comments
National Institutes of Health Traumatic Coma Databank							
Levin et al., 1991b	Severely head injured patients (defined by GCS of 8 or less at time of or during first 48 h after admission, corresponding with lack of eye-opening, lack of comprehensible speech, and inability to obey commands) admitted to four geographically diverse clinical centers	Prospective	April 1983–April 1988	1,030			

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Reference	Purpose	Study design	Population (where appropriate) Eligible	Located	Enrolled (Response rate)	Comments
Levin et al., 1991b	Vegetative state, and consciousness	Prospective	650 patients available for analysis after following exclusions: 167 (16%) had gunshot wounds, 121 (14%) were brain dead on admission, 92 (12%) were under 16 years old			
Levin et al., 1991a	Intracranial hypertension in relation to memory deficits	Prospective	Intracranial pressure recorded at 6-mo followup (n = 149), 1-year followup (n = 132); 133 patients 6 mo after injury, 126 patients 1 year after injury assessed with auditory verbal and nonverbal visual memory tests			Comparison group, normal community residents of Galveston (n = 27) matched on age, education
Chesnut et al., 1993	Early and late hypotension in regards to mortality	Prospective	699 patients available for analysis at time of hospital arrival after following exclusions: 284 were brain-dead on admission, did not survive resuscitation, or had GSW to head; 29 had insufficient information on prehospital course; 18 had insufficient blood-pressure or blood-gas results			
Lu et al., 2005	Mortality	Retrospective	635 patients 16–65 years old from TCDB in 1984–1987 (163 with penetrating injury, 76 dead on arrival excluded); 382 from Medical College of Virginia and 822 from clinical-trial databases also included			

Reference	Eligible population	Type of study or methods	Date(s) of enrollment	Subgroup (n=eligible subjects)	Contacted or located (% of eligible)	Responded or enrolled (Response rate)	Comments
Bryant and Harvey Studies							
Bryant and Harvey, 1998	222 adults 16–65 years old (mild TBI, no TBI) admitted to major trauma center in New South Wales, Australia after MVA	Prospective	Unspecified 10-mo period	98 had mild TBI;	79 (81%) included	At 6 mo, 63 patients captured (80% followup rate)	Exclusion criteria: inability to speak English, PTA > 24 h, not medically fit or on narcotic analgesia other than codeine, inability to be contacted

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Reference	Purpose	Study design	Population (where appropriate)			Comments
			Eligible	Located	Enrolled (Response rate)	
Bryant and Harvey, 1999a	Influence of mild TBI on acute stress disorder, PTSD	Prospective	222 patients admitted during 10-mo period; 79 patients with TBI, 92 without TBI included in study; at 6-mo followup, 63 (80%) mild-TBI patients, 71 (77%) non-TBI patients eligible			
Harvey and Bryant, 2000	Relationship between acute stress disorder and PTSD after MTBI	Prospective	2-year assessment of mild-TBI study population from Bryant 1998; 50 mild-TBI patients captured (63% retention rate from original population, 79% retention from 6-mo population)			
Bryant and Harvey, 1999b	PTSD, PCS	Prospective	145 of admitted patients during study period; 46 mild-TBI patients, 59 no-TBI patients captured at 6-mo assessment (83% of eligible sample)			

Reference	Eligible population	Type of study or methods	Date(s) of enrollment	Subgroup (n=eligible subjects)	Contacted or located (% of eligible)	Responded or enrolled (Response rate)	Comments
University of Washington Longitudinal Traumatic Brain Injury Studies							
Behavioral Outcome in Head Injury, McLean et al., 1993	Consecutively-admitted adults to Level I trauma center at Harborview; subjects met following criteria: any period of loss of consciousness, PTA for at least 1 h, or other objective evidence of head trauma; injury had to require hospitalization; age range, 15–60 years; patients with pre-existing conditions excluded; 102 friend controls included in study	Prospective cohort	1980–1982	102			English speaking adults; enrolled at time of injury and prospectively followed to 1 year; of 102 enrolled and examined at 1 month, 97 examined at 1 year

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Reference	Eligible population	Type of study or methods	Date(s) of enrollment	Subgroup (n=eligible subjects)	Contacted or located (% of eligible)	Responded or enrolled (Response rate)	Comments
Patient Charecteristics and Head Injury Outcome, Temkin et al., 1990; Dacey et al., 1991	Consecutively admitted adults to Level I trauma center at Harborview; subjects admitted with TBI and met following criteria: any period of LOC, PTA of 1 h or more or other objective evidence of cerebral trauma; subjects had to be at least 15 years old; 132 trauma controls included in study	Prospective cohort	1984–1986	352 eligible survivors		242 (69 %)	English speaking adults; 221 of 242 (91%) followed to 1 year after injury; subjects not excluded if they had pre-existing conditions
Dilantin Prophylaxis of Post-Traumatic Seizures, Temkin et al., 1990; Dikmen et al., 1991	Consecutively admitted head injured adults to Level I trauma center at Harborview; subjects met one or more of following criteria: GCS score of 10 or below, cortical contusion documented on CT, depressed skull fracture, subdural hematoma, epidural hematoma, traumatic intracerebral hematoma, penetrating head wound, or seizure within 24 h after injury	Prospective cohort	1983-1987	234 survivors		170 (73%)	English speaking adults; 137 of 170 (81%) followed to 1 year after injury; subjects with pre-existing conditions excluded; subjects had to be at least 15 years old

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Reference	Eligible population	Type of study or methods	Date(s) of enrollment	Subgroup (n=eligible subjects)	Contacted or located (% of eligible)	Responded or enrolled (Response rate)	Comments
Valproate Prophylaxis of Post-Traumatic Seizures, Temkin et al., 1999a; Dikmen et al., 2000	English-speaking adults admitted to level 1 trauma center at Harborview Medical Center in Seattle, WA; subjects consecutively admitted with TBI and met one or more of following criteria: cortical contusion, depressed skull fracture, subdural hematoma, epidural hematoma, intra-cerebral hematoma, penetrating head wound, or a seizure within first 24 h after injury; subjects had to be at least 18 years old; subjects excluded if they had pre-existing conditions	Prospective cohort	1991-1995	342 survivors			273 of 342 (80%) survivors seen 6 mo after injury, 212 of 281 (75%) survivors seen 1 year after injury; denominator changed at 1 year because of study decision to suspend 1-year testing in last 61 cases

Reference	Purpose	Study design	Population (where appropriate)			Comments
			Eligible	Located	Enrolled (Response rate)	
Dikmen et al., 1986	Neuropsychologic, social outcomes of mild TBI	Prospective cohort	20 hospitalized subjects with mild head injury; 19 uninjured friend controls; subjects with pre-existing conditions excluded; subjects were from Behavioral Outcome in Head Injury study			19 of 20 (95 %) mild head injured seen at 1 year; healthy friend controls may not control for general effects of trauma

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Reference	Purpose	Study design	Population (where appropriate)			Comments
			Eligible	Located	Enrolled (Response rate)	
Dikmen et al., 1987	Memory	Prospective cohort	102 closed head-injured patients selected from Behavioral Outcome of Head Injury study; 102 friend controls; no pre-existing conditions			97 of 102 head-injured subjects evaluated 1 year after injury
Fraser et al., 1988	Comparison of people with TBI who had returned to work at 1 year and those who had not returned in neuropsychologic, psychosocial functioning at 1 mo, 1 year after injury	Prospective cohort	48 of 102 closed head-injured patients selected from Behavioral Outcome of Head Injury study who were working for more than 4 h/day for at least 5 mo before injury; 102 friend controls; no pre-existing conditions			All 48 followed to 1 year after injury
Dikmen et al., 1990	Neuropsychologic outcomes	Prospective cohort	31 adults with moderate or severe head injury investigated over 2 years (subgroup of sample of 102 consecutive head injured patients selected from Behavioral Outcome of Head Injury study); 102 noninjured friend controls)			Subgroup analyses based on small samples 31 of 46 (67%) eligible subjects from Behavioral Outcome of Head Injury study followed to 2 years after injury; no significant differences between 31 who completed 2-year followup and 15 who were lost on demographics and neuropsychologic measures at 1 and 12 mo after injury

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Reference	Purpose	Study design	Population (where appropriate)			Comments
			Eligible	Located	Enrolled (Response rate)	
Dikmen et al., 1993	Psychosocial outcomes	Prospective cohort	31 adults with moderate or severe head injury investigated over 2 years (subgroup of sample of 102 consecutive head injured patients selected from Behavioral Outcome of Head Injury study, 102 noninjured friend controls			31 of 46 (67%) eligible from Behavioral Outcome of Head Injury study followed to 2 years after injury; no significant differences between 31 who completed 2-year followup and 15 who were lost on demographics or neurologic severity indexes
McLean et al., 1993	Psychosocial outcomes; Sickness Impact Profile; Head Injury Symptom Checklist; Modified Function Status Index	Prospective cohort	102 consecutive head injured patients from Behavioral Outcome of Head Injury study, 102 noninjured friend controls			Followed 97 of 102 (95%) to 1-year after injury; Subgroup analyses based on small samples
Dikmen et al., 1994	Time to return to work	Prospective cohort	366 head injured individuals from 3 prospective, longitudinal studies (Behavioral Outcome of Head Injury, Patient Characteristics and Head Injury Outcome, Dilantin Prophylaxis of Post-Traumatic Seizures) Mean age, 30 years; mean education, 12 years; 77% male, 89% white; 75% working over 20 h/week before injury 95 trauma controls from Patient Characteristics and Head Injury Outcome study; mean age, 31 years; mean education, 12 years; 75% male; 81% white; 78% working over 20 h/week before injury			Head injured and controls similar on demographics, preinjury employment status, types of jobs held; Results presented as weighted averages to adjust for differences in eligibility criteria between studies

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Reference	Purpose	Study design	Population (where appropriate)			Comments
			Eligible	Located	Enrolled (Response rate)	
Haaland et al., 1994	Motor skills	Prospective cohort	40 patients selected from 102 consecutive head injured patients selected from Behavioral Outcome of Head Injury study who did not have peripheral upper body injuries, 88 healthy friend controls			40 of 58 selected with no peripheral injuries, had complete data at 1 mo and 1 year after injury; 18 cases presumably excluded primarily because neurologically too impaired to be tested at 1 mo
Dikmen et al., 1995a	Preinjury drinking, blood alcohol level; preinjury, postinjury patterns of alcohol use	Prospective cohort	197 head injured patients from Patient Characteristics and Head Injury Outcome study			179 of 197 (91%) followed until 1 year after injury; 89 also participated in Dilantin Prophylaxis of Post-Traumatic Seizures study and told by study nurse that they should not drink alcohol
Dikmen et al., 1995b	Neuropsychologic outcomes	Prospective cohort	436 adult head injured patients recruited at time of injury in 3 prospective, longitudinal studies (Behavioral Outcome in Head Injury, Patient Characteristics and Head Injury Outcome, Dilantin Prophylaxis of Post-Traumatic Seizures); 121 general trauma controls enrolled as part of Patient Characteristics and Head Injury Outcome study			Study subjects included 85% of 514 subjects recruited from 3 studies; results as weighted averages to adjust for differences in eligibility criteria

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Reference	Purpose	Study design	Population (where appropriate) Eligible	Located	Enrolled (Response rate)	Comments
Dikmen et al., 1995c	Global outcome, independent living, employment, income, Sickness Impact Profile	Prospective cohort	466 subjects with TBI selected from 3 prospective, longitudinal studies (Behavioral Outcome in Head Injury, Patient Characteristics and Head Injury Outcome, and Dilantin Prophylaxis of Post-Traumatic Seizures) 124 trauma controls who had bodily injury other than to head 88 friend controls, friends of TBI patients, with no pre-existing conditions			91% of 514 subjects followed to 1 year after injury Results presented as weighted averages to adjust for differences in eligibility criteria between studies
Doctor et al., 2005	Employment status	Prospective cohort	418 TBI working before injury from 4 longitudinal investigations enrolled 1980–1994 (Behavioral Outcome in Head Injury, Patient Characteristics and Head Injury Outcome, Dilantin Prophylaxis of Post-Traumatic Seizures, Valproate Prophylaxis of Post-Traumatic Seizures.			374 of 418 (89%) followed to 1 year after injury

Reference	Eligible population	Type of study or methods	Date(s) of enrollment	Subgroup (n=eligible subjects)	Contacted or located (% of eligible)	Responded or enrolled (Response rate)	Comments
Roberts (Radcliffe, UK) Studies							
Roberts, 1979	548 people (from total population of 7,000) 5–83 years old who sustained TBI and remained unconscious or amnestic >1 week admitted to Radcliffe Infirmary, Oxford: 479 admitted directly of accident (consecutive series), 69 transfers from Addenbrook Hospital, Cambridge	Prospective	1948–1961				11 lost to followup, 206 died, leaving 331 surviving patients (291 from consecutive series, 40 from selected series)

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Reference	Eligible population	Type of study or methods	Date(s) of enrollment	Subgroup (n=eligible subjects)	Contacted or located (% of eligible)	Responded or enrolled (Response rate)	Comments

Reference	Purpose	Study design	Population (where appropriate)			Comments
			Eligible	Located	Enrolled (Response rate)	
Roberts, 1979	Hypothalamic, pituitary dysfunction	Prospective	291 patients from consecutive series			
Roberts, 1979	Positional vertigo, headaches	Prospective	291 patients from consecutive series			
Roberts, 1979	Epilepsy	Prospective	291 patients from consecutive series			
Lewin et al., 1979	Epilepsy, mortality	Prospective, retrospective	291 patients from consecutive series, 75 patients in whom cause of death was determined			

Reference	Eligible population	Type of study or methods	Date(s) of enrollment	Subgroup (n=eligible subjects)	Contacted or located (% of eligible)	Responded or enrolled (Response rate)	Comments
Jennett (Oxford, Rotterdam, Cardiff, and Manchester) Studies							
Jennett and Lewin, 1960	Oxford series: 1,000 head-injured patients with at least brief period of unconsciousness	Prospective, retrospective	November 1948–February 1952				821 unselected patients admitted directly from accident site; 179 selected patients transferred from other hospitals—these cases were considered more severe and complicated

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Reference	Purpose	Study design	Population (where appropriate)			Comments
			Eligible	Located	Enrolled (Response rate)	
Jennett, 1969	Epilepsy	Prospective	189 patients from Oxford series, cases from Lewin; 150 patients from Glasgow series epileptic within 8 weeks after injury; 73 patients with missile injuries as comparison group; 333 patients 1 year after injury, 219 patients 4 years after injury with depressed fractures from Oxford and Glasgow series			
Jennett, 1962	Epilepsy	Prospective	381 patients who had blunt head injuries followed by early epilepsy (n = 139), late epilepsy (n = 282) drawn from Oxford series (additional patients captured outside study dates), Manchester and Cardiff, UK			
Jennett, 1973	Epilepsy	Prospective	Patients with known risk factors for late epilepsy—early epilepsy, intracranial hematoma (evacuation within 14 days of injury), depressed fracture—drawn from Oxford series, Glasgow series; 250 patients with depressed fractures from Rotterdam			
Jennett, 1975	Epilepsy	Prospective	Summary of previous data and findings			

Reference	Eligible population	Type of study or methods	Date(s) of enrollment	Subgroup (n=eligible subjects)	Contacted or located (% of eligible)	Responded or enrolled (Response rate)	Comments
Football Players: Guskiewicz et al. 2005, 2007							
Guskiewicz et al., 2005	All 3,683 living members of National Football League Retired Players Association	Retrospective cohort	2001–2002	3,683	2,552	2,552	

Reference	Purpose	Study design	Population (where appropriate)			Comments
			Eligible	Located	Enrolled (Response rate)	
Guskiewicz et al., 2007	Depression	Retrospective cohort	2,552 (69%) responded to questionnaires			

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Reference	Eligible population	Type of study or methods	Date(s) of enrollment	Subgroup (n=eligible subjects)	Contacted or located (% of eligible)	Responded or enrolled (Response rate)	Comments
Boxing Studies: Porter et al., 1996, 2003							
Porter and Fricker, 1996	Male boxers in amateur boxing clubs in Ireland 16–25 years old; subjects had to complete minimum of 40 bouts	Prospective, observational	1991–1992	53	53	20 selected randomly (38%)	Many lost because of strict exclusion criteria; study of boxing, not brain injury; flawed comparison group in that controls also had concussion; differentiation in rate of concussion in cases, controls Exclusion criteria: excess alcohol consumption (>20 standard drinks/week or >4 drinks/day)

Reference	Purpose	Study design	Population (where appropriate)			Comments
			Eligible	Located	Enrolled (Response rate)	
Porter, 2003	Neuropsychologic impairment	Prospective, observational	20 male boxers from amateur boxing clubs in Ireland 16–25 years old; subjects had to complete a minimum of 40 bouts 1 case and 2 controls lost to followup			See comments above

NOTE: ALS = amyotrophic lateral sclerosis, CHSA = Canadian Study of Health and Aging, CT = computed tomography, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th ed., ED = emergency department, GCS = Glasgow Coma Scale, GSW = gunshot wound, ICD-10 = International Statistical Classification of Diseases and Health Related Problems, 10th revision, LLI = lower-limb injury, LOC = loss of consciousness, MA = Massachusetts, MN = Minnesota, MS = multiple sclerosis, MTBI = mild traumatic brain injury, MVA = motor vehicle accident, PCS = postconcussion syndrome, PD = Parkinson's disease, PPCSC = predictors of postconcussion symptom complex, PTA = posttraumatic amnesia, PTSD = posttraumatic stress disorder, TBI = traumatic brain injury, TCDB = Traumatic Coma Databank, UK = United Kingdom, US = United States, VA = Veterans Affairs, VHIS = Vietnam Head Injury Study, WA = Washington

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6

NEUROCOGNITIVE OUTCOMES

This chapter highlights studies that examined outcomes related to alterations in neurocognition. Traumatic brain injury (TBI) can result in changes in neurocognitive performance as measured by tests of sensory integrity, motor speed and coordination, attention, working memory, episodic memory, processing speed, language-processing, visual-spatial processing, and executive functions (such as higher-order planning, initiating and directing, monitoring, problem-solving, and inhibitory control). Findings of alterations in neurocognitive performance were carefully examined by the committee; there were over 430 studies of TBI and neurocognitive outcomes in the committee's database. The committee chose studies that specifically answered the question related to its charge, that is, what long-term outcomes (lasting longer than 6 months) might be associated with a penetrating or closed head injury in adults and meet the general criteria for inclusion described in Chapter 4. The term "neurocognitive outcome" as used in this chapter refers to cognitive impairment while the word neuropsychologic refers to the kinds of measurements most studies utilized to determine the level of impairment.

With regard to penetrating brain injury, it has been determined that the location of a brain injury and the volume of brain tissue lost affect the type and extent of neurocognitive deficits. Many scholarly articles and textbook chapters have described the relationship of localization of brain injury with specific outcomes (Damasio et al., 1994; Haas, 2001; Ratiu et al., 2004; Silver et al., 2005; Raymont et al., 2008), so it will not be discussed here.

The chapter first discusses outcomes related to penetrating head injury and then outcomes related to closed head injury. Conclusions follow each section; the conclusions that follow the closed head injury section are further delineated by the severity of the injury.

PENETRATING BRAIN INJURY

Studies of penetrating brain injuries have been conducted primarily in military populations and are useful because they have long-term followup and preinjury neurocognitive-test information. Primary studies are presented first, followed by secondary studies, a summary and conclusion, and finally a table (Table 5.1) with information abstracted from the primary studies.

Chapter 5 provides a detailed overview of many of the studies of military populations who have been injured during war.. Some of the studies inform the discussion of long-term outcomes; others were not designed to answer the question posed to the committee regarding long-term sequelae of brain injury. The committee included the military studies that fit its task best; some of the studies are primary and others secondary, but they are all described in Chapter 5. The committee identified five primary studies of penetrating brain injury, and they are discussed below.

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Primary Studies

Teuber and Weinstein (1954) (see cohort description in Chapter 5) studied 35 World War II veterans selected from 185 veterans who had penetrating missile injuries and loss of brain tissue and 12 controls from 101 veterans who had missile injuries of peripheral nerves but no brain injury. All veterans had sustained their injuries 5–8 years before the study. The 35 brain-injured were selected by identifying equal numbers of men with injuries in the anterior or posterior one-third of the brain and in the right or left hemisphere. The control group consisted of nine men with arm injuries and three with leg injuries. All the men were tested with the Seguin-Goddard Formboard Test, which was administered with the men blindfolded first in its normal position and then after a 180-degree rotation. Men with brain injuries took more time, made more errors, and recalled fewer forms than the controls.

Another study by Weinstein and Teuber (1957b) examined two groups of men: 62 who had loss of cerebral tissue due to penetrating head injury and 50 who had trauma of peripheral nerves. Preinjury Army General Classification Test (AGCT) scores, which had been administered on induction into the Army 13–15 years before the study, were available for all the men. Preinjury education level was determined by interview and from case records. The civilian edition of the AGCT was administered to all the study participants 10–12 years after their injuries. The findings indicate clearly that the change in AGCT score was significantly worse in the penetrating-injury group than in the peripheral-nerve–injured group. Furthermore, although the primary aim of the study was to investigate the connection between preinjury education and intelligence and intellectual deterioration after brain injury, the authors note that the findings were independent of any effects of differences in preinjury education or preinjury AGCT score.

Corkin et al. (1989) conducted a 30-year longitudinal study of 84 World War II veterans to determine the cognitive effects of penetrating head injury: 57 veterans who had penetrating head injury and 27 veterans who had peripheral nerve injury who were matched with respect to age and premorbid intelligence and education. The veterans were examined in the 1950s and in the 1980s. The veterans selected were those who had been seen by Teuber and Weinstein in New York (see Chapter 5 for Teuber's cohort of World War II veterans). Both groups of veterans had received an average of 12 years of education before injury and were tested with the AGCT before injury. Total scores of 42 veterans were available from military records. Review of the preinjury AGCT total scores showed no differences between the two groups. Both groups were given two cognitive tests after injury: the AGCT and the Hidden Figures Test. The AGCT contains three subscales—vocabulary, arithmetic, and block-counting—and the Hidden Figures Test measures the ability to discriminate figures from background. Ten years after the end of the war, in the 1950s, the penetrating-injury group showed poorer performance on both cognitive tests than the peripheral-nerve–injured controls. Forty years after the war, in the 1980s (when the study was conducted), the penetrating-injury group exhibited even poorer performance on every cognitive measure except vocabulary, which remained constant. When the data were examined by brain region with computed tomography, the site of the injury exerted an even stronger effect. Veterans with injuries of the left parietal lobe had a significantly greater decrease on the vocabulary and arithmetic subscales, and those with lesions in other brain regions showed a greater decrease on other subscales or on the Hidden Figures Tests. Penetrating-injury subjects lost an average of 7.9 points from the 1950s to the 1980s, and those with peripheral nerve injury gained an average of 0.4 point. The decline was most pronounced in older subjects. The results suggested accelerated aging in those with penetrating head injury.

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As part of the Vietnam Head Injury Study (VHIS; see Chapter 5 for description of the study and the cohort), Grafman et al. (1988) studied the nature of intellectual function after penetrating missile wounds. The cohort consisted of 263 men who had penetrating brain injuries—96 with lesions in the right hemisphere, 78 in the left hemisphere, and 89 in both—and 64 uninjured controls who met the inclusion criteria: they served in Vietnam during the same years as the brain-injured, and they were stratified according to preinjury Armed Forces Qualification Test (AFQT) to be matched with the brain-injured. There were no significant differences between the groups in age, education, or preinjury AFQT percentile scores. Although Grafman and colleagues stratified head-injured subjects by location of brain injury, the study data clearly indicate that the head-injured showed worse change than the controls in performance on the AFQT. The authors also assessed whether brain-volume loss correlated with changes in cognitive function. As expected, greater total brain-volume loss correlated with greater declines in AFQT scores from before to after injury ($p < 0.0001$). The authors examined whether lesion location was associated with cognitive decline. No significant effects on AFQT scores by lesion location (right, left, or bilateral) were observed. Preinjury education level also did not correlate with AFQT. The results indicated several factors that influence cognitive decline after brain injury as measured with the AFQT: preinjury intelligence was the strongest predictor of postinjury intelligence scores, followed by the size of the lesion, and then the location of the lesion. Preinjury education level did not correlate with cognitive decline.

Raymont et al. (2008) examined 182 Vietnam veterans as part of phase 3 of the VHIS. All were identified from the VHIS registry and had a history of penetrating head injury although an additional 17 patients who were assessed for phase 3 had not participated in phase 1 or 2. Controls were 32 veterans who had participated in phase 2 and an additional 23 who were recruited through advertisements in veteran publications; none of the controls had a history of head injury. All the veterans were assessed over 5–7 days at the National Naval Medical Center in Bethesda, MD. There were no significant differences between cases and controls with regard to age, years of education, or preinjury induction intelligence level (as measured with the AFQT). Brain lesions were identified with computed tomography. The median AFQT score in the entire sample was 65.0; in the penetrating-injury group, it was 54.0, and in the controls, 74.0. The penetrating-injury veterans had a significantly greater decrease in AFQT score than controls from phase 2 to phase 3 and from before injury to phase 3. The scores of the controls improved from before injury to phase 2 compared to those with penetrating head injuries. If officers were excluded from the sample, the AFQT scores of those with penetrating head injuries decreased significantly more than the scores of the controls over the entire period from before injury to phase 3. Those with penetrating injuries had lower AFQT scores at phase 3 (mean, 52.58) than the controls (mean, 68.50). The authors examined several risk factors for AFQT outcome at followup and for declining AFQT scores, including dementia, location of brain lesion, and genetic markers. They found that preinjury intelligence was the most consistent predictor of cognitive outcome at all followup times and of decline over time. There was no evidence that laterality of the lesion affected overall intelligence or decline. Specific brain regions, the degree of local and global atrophy, and some genetic markers were found to be associated with exacerbated decline. Thus, the long-term followup of Vietnam veterans with penetrating head injury found that exacerbated decline in intelligence is a significant risk.

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Secondary Studies

Like the primary studies, the secondary studies of penetrating TBI have been conducted in military cohorts (see Chapter 5), but they have methodologic limitations that prevented the committee from including them as primary studies. For example, many of the studies examined differences in specific cognitive domains as a function of the location of the brain injury or did not compare brain-injured people with a non–brain-injured control group.

Weinstein and Teuber (1957a) examined the effects of penetrating brain injury on intelligence-test scores in patients who had stable, localized brain injury. The investigators obtained preinjury AGCT scores for 62 men who later sustained penetrating brain injury and for 50 controls who incurred arm or leg nerve injuries. All the men had been injured during World War II 1–3 years after the initial AGCT. A comparable AGCT was administered about 10 years after the men were injured. The preinjury scores of the brain-injured and control groups were almost identical: means, 105.0 and 106.4, respectively. Scores on the postinjury test showed some gain: 48 of the 50 controls increased their mean score to 119.4. The 62 brain-injured men were divided into groups according to the location of their injuries: frontal, temporal, parietal, or occipital, in the left, right, or both hemispheres. The investigators found that lesions in frontal and occipital lobes were not associated with a significant decrease in scores, but lesions in the parietal and temporal lobes of the left hemisphere were associated with a significant decrease.

Weinstein et al. (1956) studied spatial orientation in 62 men who had loss of cerebral tissue because of penetrating head injury and 18 men who had leg peripheral nerve injuries. All the men had been injured during World War II (see cohort description in Chapter 5). The authors focused on a particular task of spatial orientation: finding a route on a map. Men with parietal lobe lesions (in either hemisphere) did more poorly than all the brain-injured men who did not have parietal lesions, and the men with brain damage, other than in the parietal lobe, did not perform more poorly than controls.

The VHIS has resulted in numerous publications of long-term outcomes associated with penetrating head injury (see Chapter 5). Salazar et al. (1986) found that Vietnam veterans who had penetrating injuries of the basal forebrain had worse outcomes than uninjured controls with regard to episodic memory, reasoning, and arithmetic but not on tests of intelligence, attention, and language. Several studies by Grafman et al. (for example, 1986, 1990) provided evidence of the detrimental effects of penetrating head injuries on facial discrimination (1986) and examined neurocognitive performance on the Wisconsin Card Sorting Test, noting that brain-damaged Vietnam veterans made more errors than controls (1990). Although there have been additional studies in the VHIS series, many were not designed to answer the question specifically posed to the committee regarding long-term health outcomes. The studies that do shed light on long-term outcomes, other than neurocognitive effects, are discussed elsewhere in this volume.

Summary and Conclusion

The committee reviewed five primary studies (Teuber and Weinstein, 1954; Weinstein and Teuber, 1957b; Grafman et al., 1988; Corkin et al., 1989; Raymont et al., 2008) and five secondary studies (Weinstein et al., 1956; Weinstein and Teuber, 1957a; Salazar et al., 1986; Grafman et al., 1986, 1990) of penetrating head injury in military populations. The primary and secondary studies are consistent in pointing toward a decline in neurocognitive function after penetrating head injury.

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With regard to increased errors on the form board test, Teuber and Weinstein (1954) showed that veterans who had penetrating head injury took more time, made more errors, and recalled fewer forms than the controls. A later study by Weinstein and Teuber (1957b) examined the change in AGCT score from before injury to after injury and found that subjects who had penetrating head injury had a greater decline in score than the group who had peripheral nerve injury independently of preinjury education and preinjury AGCT scores. Grafman et al. (1988) found cognitive decline after brain injury as measured the AFQT. However, preinjury intelligence score was the most predictive factor in postinjury intelligence score, followed by the size of the lesion; the location of the injury was the least important. In contrast, preinjury education level did not correlate with cognitive decline.

The study of World War II veterans by Corkin et al. (1989) demonstrated poorer performance on cognitive tests in veterans who had penetrating head injury than in controls and continued decline over 30 years in the brain-injured veterans on every cognitive measure except vocabulary, which remained constant. It was noted that the site of the injury exerted a strong effect on the type of deficits. Finally, the study of Vietnam veterans by Raymont et al. (2008) demonstrated that exacerbated decline in intelligence over 30–40 years is a significant risk for veterans with penetrating head injury.

The five secondary studies also showed long-term deficits in neurocognition including intelligence (Weinstein and Teuber, 1957a); spatial orientation (Weinstein et al., 1956); memory, reasoning, and arithmetic (Salazar et al., 1986); facial discrimination (Grafman et al., 1986); and neurocognitive decline as measured with the Wisconsin Card Sorting Test (Grafman et al., 1990).

Those studies, particularly the secondary studies, suffer from various limitations, including small samples, a focus on injury sites and localization of functional outcomes (which were outside the committee's charge), incomplete description of how subjects and controls were selected, and apparent high rates of loss of the original sample at followup times. However, the studies had advantages not seen in studies of civilian injury, including the availability of baseline cognitive test scores and the long-term nature of followup (in some cases, 40 years or more). The overall body of evidence demonstrates poor neurocognitive outcomes in people who suffer penetrating head injury.

The committee concludes, on the basis of its evaluation, that there is sufficient evidence of a relationship between sustaining a penetrating TBI and decline in neurocognitive function associated with the affected region of the brain and the volume of brain tissue lost.

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TABLE 6.1 Penetrating Head Injury and Neurocognitive Outcomes

Reference	Study Design	Population	Type of TBI: Mild, Moderate, Severe; Blunt, Penetrating, Blast	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
Teuber and Weinstein, 1954	Cohort	35 men with brain injury selected from 185 with missile wopunds of head, 12 controls with peripheral nerve injury wounds of head controls chosen from 101 with missile wounds of peripheral nerves	Penetrating missile injuries of head or peripheral nerves	Form Board Test	Brain-injured subjects took more time, made more errors, recalled fewer forms than controls		Subjects, controls sustained injuries 5–8 years before testing Subjects grouped on basis of location of lesions
Weinstein and Teuber, 1957b	Cohort	62 men with loss of cerebral tissue due to penetrating head trauma, 50 controls with peripheral nerve injury	Penetrating head trauma or peripheral nerve trauma	AGCT administered 13–15 years before injury (on induction into Army) AGCT administered again 10–12 years after injury	Controls had mean increase of 13.0 AGCT points from preinjury to postinjury testing Brain-injured group, excluding aphasics, had average increase of 5.2 points; total brain-injured group had increase of 1.6 points Education before injury did not influence extent to which performance on intelligence test was affected after injury	Eliminated men with aphasic difficulties that prevented them from reading practice-test questions	Preinjury AGCT score available for 53 subjects Preinjury educational level determined by interview and from case records

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Reference	Study Design	Population	Type of TBI: Mild, Moderate, Severe; Blunt, Penetrating, Blast	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
Corkin et al., 1989	Cohort (This population was first seen in Teuber's NY laboratory)	84 World War II veterans: 57 with penetrating head injury, 27 with peripheral nerve injury 18–34 years old at time of injury, first testing 10 years after injury (1950s), and testing 40 years after injury (1980s)	Penetrating head injury; injury severity determined by number of cortical lobes involved, presence of tantalum plate, history of seizures, use of anticonvulsant medication	AGCT (including Total, Vocabulary, Arithmetic, Block counting subscales), figure-ground discrimination (measured with Hidden Figures Test)	10 years after end of war (in 1950s), TBI group had poorer performance on both cognitive tests 30 years after war, TBI veterans, as a group, exhibited even poorer performance on every cognitive measure except vocabulary, which was constant	Matched with respect to age, premorbid intelligence, premorbid education	Existence of baseline performance, retesting at 10 and 40 years after penetrating brain injury compared with appropriate controls are strengths of study; possible limitation is how representative the subjects were of all those injured in World War II; subsamples selected from 314 studied by Teuber and Weinstein (1956, 1957); age, performance correlated only in brain-injured subjects, so age-related factors might have contributed to exacerbated decline
Grafman et al., 1988	Prospective, long-term followup of Vietnam War veterans (Part of VHIS)	263 brain-injured veterans, 64 uninjured controls matched on preinjury AFQT scores	Penetrating head injury	Cognitive-outcome, AFQT	Preinjury AFQT score was most predictive factor for postinjury intelligence scores, followed by brain-volume loss, location of injury; preinjury	ANOVAs, multiple regression analysis performed to assess association between size and location of	

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Reference	Study Design	Population	Type of TBI: Mild, Moderate, Severe; Blunt, Penetrating, Blast	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
					education level not associated with cognitive decline	brain lesions predicted cognitive function after injury	
Raymont, 2008	Prospective, long-term followup of Vietnam War Veterans (part of VHIS phase 3) 2,000 patients entered in registry in 1967–1970	Subjects drawn from VHIS registry; 92% had penetrating head injury; of 520 from phase 2, 484 are still alive, and 182 attended phase 3	Penetrating head injury	Cognitive-outcome, AFQT	At phase 3, no significant differences between head-injured and controls in age, education, intelligence The more global the cognitive test, the greater the effect of brain-volume loss	ANOVAs, linear logistic and stepwise multiple regression procedures preformed to assess impact of demographic factors, preinjury intelligence, brain-volume loss, lesion location, genetic markers on cognitive ability 36–39 years after injury	Those with penetrating head injury had lower AFQT scores at phase 3 than controls, significantly greater decrease in AFQT score than controls from phase 2 to phase 3 and from preinjury to phase 3; when impact of education, preinjury intelligence, brain volume loss, lesion location on postinjury intelligence was examined, most important determinant of postinjury intelligence was preinjury performance as measured by AFQT

NOTE: AFQT = Armed Forces Qualification Test, AGCT = Army General Classification Test, ANOVA = analysis of variance, TBI = traumatic brain injury, VHIS = Vietnam Head Injury Study.

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CLOSED HEAD INJURY

This section focuses on studies of closed (nonpenetrating) head injuries. These injuries are typically categorized as mild, moderate, or severe TBI. One of the problems encountered by the committee in evaluating studies of closed TBI is the difficulty in comparing severity of TBI among studies. Papers are inconsistent in the measurement of severity, particularly of moderate TBI.

As in the previous section, primary studies are presented first and followed by secondary studies, a summary and conclusions, and finally a table (Table 5-2) with information abstracted from the primary studies.

Primary Studies

The committee selected six primary studies of closed head injury. They differ from the studies of penetrating head injury in that they examined civilian populations with TBI resulting from motor-vehicle crashes, falls, assaults, or sports activities.

A study by Dikmen et al. (1986), using a cohort from the trauma center at Harborview Medical Center in Seattle, WA (previously described in Chapter 5), examined neurocognitive outcomes after mild TBI. The head-injured, drawn from a larger cohort, were 20 consecutive patients 15–60 years old who had mild TBI. The 19 controls were friends of the TBI patients from the larger head-injured group (see Chapter 5) who were matched with regard to age, education, and sex; exclusionary criteria included evidence of preinjury central nervous system (CNS) disease or alcoholism. Neuropsychologic tests were administered at 1 month and 12 months after injury; controls were tested at the same intervals. The Halstead-Reitan Neuropsychological Test Battery and additional measures of memory were administered. The head-injured group performed slightly less well than the uninjured group on two of the 21 measures (the Seashore Rhythm Test and the Selective Reminding Test) at 1 month after injury. At 1 year, none of the neuropsychologic measures showed significant differences. Thus, although subtle neuropsychologic effects were found at 1 month after a mild TBI, they could no longer be detected at 1 year.

In another study by Dikmen et al. (1987) (see Chapter 5), the relationship between injury severity and memory was examined in 102 consecutive head-injured patients admitted into Harborview Medical Center. All patients had sustained blunt head injury; most of the cases were mild or moderate. The uninjured comparison group consisted of 102 friends of the head-injured matched on age, education, race, and sex. Head-injury severity was measured with the Glasgow Coma Scale (GCS), assessed within 24 hours of injury to determine the depth of coma; time from injury to consistent ability to follow simple commands (TFC), used as an index of coma length; and posttraumatic amnesia (PTA), used to determine the length of impaired consciousness. The Wechsler Memory Scale (WMS) and the Selective Reminding Test (SRT) were used at 1 and 12 months after injury. The head-injured group performed more poorly than the uninjured controls ($p < 0.001$) on each of the subscales of the WMS and the SRT. Similarly, at 1 year, there was significant impairment on most subscales of the tests administered. However, head- injured patients performed better at 1 year than at 1 month. With regard to severity of

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injury, only those with deep or prolonged impaired consciousness (TFC over 1 day, PTA at least 14 days, and GCS less than 8) were performing significantly worse at 1 year than the controls.

Dikmen et al. (1995) conducted a prospective study of 436 adults with mild, moderate, or severe TBI recruited at the time of injury from Harborview Medical Center, a level 1 trauma center (see Chapter 5). The study included English-speaking adults who had TBI with loss of consciousness for any period or PTA for at least 1 hour or with objective evidence of TBI (such as hematoma) and who were hospitalized and survived at least 1 month after injury. Most TBI patients (74%) had sustained their injuries in motor-vehicle crashes (car or motorcycle drive, pedestrian, or bicyclist), 11% in falls, 8% in fights or assaults, and the remaining 6% in other activities. Controls were 121 patients admitted into the emergency room at Harborview Medical Center after injury to any part of the body except the head and matched to the TBI cases on age, sex, and education. Subjects and controls received a neuropsychologic assessment at 1 year after injury, which included the Halstead-Reitan Neuropsychological Test Battery and additional measures of attention and memory. The battery evaluated various neuropsychologic functions, including sensory and motor skills, attention, concentration, memory, verbal and visual-spatial intellectual skills, and executive function, such as problem-solving and flexibility of thinking. A year after injury, the TBI group performed significantly worse than controls on 18 of the 21 measures used for comparison. There was a dose–response relationship: longer coma (from time of injury to consistently following commands) was associated with greater neurocognitive impairment. Fifty percent of the subjects with the most severe TBI (those with TFC of 29 days or longer) were cognitively too impaired even to be formally tested.

Tate et al. (1991) studied a consecutive series of 87 of 100 patients who had severe TBI and were admitted into a rehabilitation facility in Australia. The patients, 15–45 years old, were compared with sibling controls on 15 factors related to various neurobehavioral impairments. Of the TBI patients, 70% had current and clinically significant impairments. Disorders of learning and memory were the most common findings 6 years after injury and differed between TBI patients (56.5%) and controls (5%). Disturbances in basic neurocognition (such as orientation, visual perception, dyspraxia, and language) were least frequent (16.5% in TBI patients and 2.5% in controls). Slowness in information processing was found in 34.1 % of the TBI patients and 2.5% of the controls, and posttraumatic personality changes were found in 40% of the TBI patients, while only 7.5% of the controls exhibited personality changes. The differences appear large, but the authors did not provide tests of their significance.

Lannoo et al. (1998) examined neurocognitive outcomes in 85 consecutive patients who had moderate to severe head injury and were admitted into the intensive-care unit (ICU) of the University Hospital of Ghent in Belgium from September 1993 to February 1996 with a GCS score of 3–12. The patients were 15–65 years old and had no previous history of CNS disease or mental retardation. The control group consisted of 32 trauma patients who had injuries of the body but not the head and were admitted into the ICU during the same study period. The controls were also 15–65 years old and had no previous history of CNS disease or mental retardation. Neuropsychologic testing was completed at 6 months after injury in 79 of the TBI patients (93%) and 22 of the controls (69%). The neuropsychologic test battery consisted of measures of attention and information processing, visual reaction time, memory and learning, verbal fluency, and mental flexibility. A multivariate analysis of variance on neuropsychologic test performance revealed that the TBI group performed significantly below the control group at 6 months after injury on most of the test measures.

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Heitger et al. (2006) studied 37 patients who had mild TBI and presented to Christchurch Hospital, New Zealand, and compared them with 37 controls individually matched to each case with respect to age, sex, and years of formal education. The controls were volunteers recruited through a database at the Department of Psychology of the University of Canterbury, Christchurch, New Zealand. Patients and controls were assessed at 1 week, 3 months, and 6 months injury; and 31 pairs were at 12 months after injury. Neurocognitive assessments included tests of attention, working memory, episodic memory, and speed of information processing and used the Paced Auditory Serial Addition Test, the California Verbal Learning Test-I (CVLT-I), the Symbol Digit Modalities Test, and the Trail Making Test. General cognitive performance was evaluated with the vocabulary and matrix-reasoning subtests of the Wechsler Abbreviated Scale of Intelligence. Results at 3 and 6 months showed deficits in verbal learning in the mild-TBI group, but results of neurocognitive tests at 12 months showed no deficits except for a marginal difference on the CVLT total standard score ($p < 0.07$).

Secondary Studies

The committee chose 17 secondary studies for review. The studies discussed here did not meet the committee's criteria for primary studies as described in Chapter 4. In this discussion, the studies are grouped as follows: TBI associated with sports and then mild TBI, moderate or severe TBI, and varied severity typically in populations other than athletes.

Traumatic Brain Injury Associated with Sports

People involved in various sports may suffer repeated head injuries, including concussions and mild TBIs. It is often difficult to determine whether the outcome of an injury is related to a single incident or to repeated incidents. When TBI is determined retrospectively by self-report, especially after a period of months or years, it is difficult to be certain about the reliability and validity of the report; this is the case particularly in sports injuries.

Studies of TBI associated with sports have found some evidence of long-term cognitive dysfunction (Moser et al., 2005; Matser et al., 1998, 1999, 2001; Wall et al., 2006; Guskiewicz et al., 2005), but the findings are not entirely consistent (Straume-Naesheim et al., 2005). Moser et al. (2005) studied 223 high-school athletes (13–19 years old) who participated in a variety of sports (primarily ice hockey, football, field hockey, lacrosse, and soccer). The authors sought to identify the long-term effects of self-reported concussion on neuropsychologic functioning by determining whether there were any differences among four groups of athletes: the recently concussed (within 1 week of neuropsychologic testing), those with no concussion history, those with one concussion sustained at least 6 months previously, and those with two or more concussions sustained at least 6 months previously. The results indicated significant differences among the groups in attention ($p = 0.012$) and cognitive flexibility and executive functioning ($p = 0.006$). Post hoc analysis demonstrated that recently concussed athletes perform worse on the attention measure than athletes with no concussion history or a history of one concussion and worse on the cognitive-flexibility measure than those with no concussion history. There were no differences between those with recent concussions and those with two or more concussions on any measures; the authors suggest that this indicates long-term neuropsychologic effects in those with multiple concussions. However, the authors do not report significant differences between athletes with two or more concussions and those with no concussion or one concussion, so their conclusions are uninterpretable.

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Matser et al. (1998, 1999, 2001) has conducted a series of studies to determine the effects of heading on neurocognitive outcomes in soccer players. They assessed neurocognitive impairment in 53 active professional soccer players and compared it with that in 27 elite noncontact-sports athletes matched on age (Matser et al., 1998). Professional soccer players performed worse than controls on neurocognitive tests of planning, memory, and visuoperceptual tasks. In another study (Matser et al., 1999), they examined 33 amateur soccer players and compared them with 27 amateur swimming and track athletes. The soccer players demonstrated poorer outcomes than the controls in planning (39% vs 13%; $p = 0.001$) and memory (27% vs 7%; $p = 0.004$). The number of concussions was inversely related to neurocognitve performance on six of the tests. Finally, Matser et al. (2001) assessed 84 active professional soccer players with respect to the number of lifetime concussions and headers (calculated as the product of the number of headers in a single match and the number of matches in the last season). The number of headers in one season was inversely related to scores on tests of focused attention and memory. The number of concussions was inversely related to scores on tests of sustained attention and visuoperceptual processing. However, it is possible that soccer players and people who participate in other sports are different before their participation, so those results do not clearly indicate that soccer-playing affects neurocognitive performance.

In contrast, Straume-Naesheim et al. (2005) studied the effect of self-reported previous concussions and heading on performance of 271 Norwegian football (soccer) players on neuropsychologic tests and did not find a relationship. Concussion was defined as loss of consciousness or amnesia after a head injury. One hundred thirty-seven players reported having one or more previous concussions, and 112 of them reported that the concussion was football-related. The results showed no relationship between total number of previous concussions or number of headings and results on neuropsychologic subtests. Furthermore, there was no difference in neuropsychologic test scores between players with the lowest heading frequency and those with the highest frequency. When those who reported never having a concussion were compared with those who reported three or more previous concussions, there were no differences in neuropsychologic performance. Thus, the authors found that lifetime heading exposure was not associated with neuropsychologic test performance.

Wall et al. (2006) studied the effects of self-reported single and repeated concussions on neurocognitive outcomes in jockeys. Data were collected on 698 jockeys licensed in the United Kingdom, and 627 participated in the study. Time from concussion ranged from 4 months to 27 years (mean, 6.45 years; standard deviation [SD], 6.33 years). Test results were compared for no concussion, single concussion, and multiple concussions. Jockeys with multiple concussions did worse than jockeys with a single concussion on a test of attention and executive functioning (Stroop Test), and younger athletes had a high risk of such decrements.

Guskiewicz et al. (2005) studied the association between repeated concussion and long-term cognitive impairment in retired professional football players (average age, 53.8 years). General health questionnaires were mailed to 3,683 retired players, and 2,552 were completed. About 61% of the players reported at least one concussion and 24% reported three or more concussions. Of the more than half the players reporting a concussion, 54% reported loss of consciousness or memory loss associated with their concussions. A second questionnaire focusing on memory and issues related to mild cognitive impairment (MCI) was sent about 4 months after the initial questionnaire and was completed by a subset of 758 retired players; the same questionnaire was also sent to a spouse or close relative of each. On the basis of statistical

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analysis of the data, the authors concluded that there is an association between recurrent concussion and clinically diagnosed MCI ($p = 0.02$) and self-reported memory problems ($p = 0.001$). Furthermore, a fivefold prevalence of MCI diagnosis and a threefold prevalence of memory problems were found in retired players who had three or more reported concussions compared with retired players who had no concussion history.

Studies conducted to examine whether boxing is associated with chronic brain damage have typically compared neurocognitive functioning between boxers and other sports groups. The results have generally not found evidence of neuropsychologic impairment in boxers. For example, Murelius and Haglund (1991) examined 50 Swedish former amateur boxers, 25 soccer players who had reported heading during their careers, and 25 track and field athletes with no previous head injury. Boxers who had taken part in many bouts had slightly lower scores on a motor measure (finger-tapping) than soccer players and track and field athletes, but overall the boxers did not have significant cognitive impairment. Butler et al. (1993) studied 86 active amateur boxers (mean age, 16.7 years), 31 amateur water polo players, and 47 rugby players matched for age but not education. Neurocognitive function was assessed before competition (or before a bout for boxers), immediately after competition, and up to 2 years later. The results before competition found significant differences on eight of the 12 tests, all indicating that boxers performed less well than the controls. Further analysis indicated that the results were not due to impairment associated with a prior history of boxing. The authors considered the findings as possibly due to uncontrolled-for differences in educational level or verbal functioning between the groups. The results soon after competition and at followup showed no evidence of neurocognitive dysfunction in amateur boxers compared with water polo and rugby players.

Porter and Fricker (1996) conducted a neuropsychologic assessment of 20 amateur boxers and compared them with 20 controls matched for age and socioeconomic status. To be eligible to enroll in the study, each amateur boxer had to have competed in at least 40 amateur matches. The subjects were evaluated initially in 1992 and then 15–18 months later. The baseline assessment showed that the boxers performed significantly worse than the controls on a motor measure with the nondominant hand and significantly better than the controls on a test of attention (Trails A) and on a test of cognitive flexibility and executive functioning (Trails B). The results remained the same at followup except that the boxers also performed significantly worse than controls on a motor measure using the dominant hand. The authors concluded that there was no evidence of neuropsychologic impairment in the amateur boxers compared with the controls, and they found no association between boxing and performance on any of the neuropsychologic tests. Porter (2003) conducted a followup study of the same population of 20 amateur boxers and 20 matched controls at 4, 7, and 9 years after the baseline evaluation. The results remained the same as reported at the 18-month evaluation. The authors found no evidence of neuropsychologic impairment over the 9-year period. In fact, the boxers improved on some of the tests in comparison with the controls.

As in much of the sports literature discussed above, a diagnosis of TBI was generally based on self-reports of exposure (for example, questionnaires that asked about number of concussions in the past or number of headings in previous matches) or surrogates of exposure (such as number of games played). Reliance on self reports of exposure may introduce recall bias, and this should be considered in evaluating the results of the studies. An additional problem is the appropriateness of the control groups used. Typically, the controls have been selected from participants in other sports or from healthy persons with unknown comparability of cognitive

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functioning before injury or before exposure. The problem here is that demographic differences between the groups may have predated the exposures and potential TBIs, and this would make interpretation of results difficult.

Mild Traumatic Brain Injury

Vanderploeg et al. (2005) examined long-term neurocognitive outcomes of self-reported mild TBI in a nonreferred sample of male veterans. The study was a cross-sectional cohort of veterans derived from the Vietnam Experience Study (see Chapter 5). Veterans were questioned about health-related events that may have occurred any time in the roughly 16 years from military discharge to the time of the study. A subsample of veterans (excluding 40 who were hospitalized after injury and the 38 on whom data were incomplete data) were categorized into three groups based on subjects' responses on a questionnaire: no history of motor-vehicle accident (MVA) and no history of TBI (normal controls, n = 3,214), injured in an MVA but no history of TBI (MVA controls, n = 539), and TBI with altered consciousness (mild TBI, n = 254). A 15-measure neuropsychologic battery and neurologic tests of tandem gait and peripheral visual attention were administered. Results revealed no statistically significant difference in any of the neuropsychologic measures among the three groups. However, on the basis of further exploratory analyses of the data, the authors concluded that the mild-TBI group showed more proactive interference on the verbal-learning measure and a tendency to give up more than controls on difficult attention tasks. The results of the study are limited by the long retrospective, self-reporting nature of the data, which could introduce considerable error.

Moderate or Severe Traumatic Brain Injury

Ruff et al. (1986) assessed neurocognitive functioning after TBI in 15 patients who had moderate TBI (GCS, 9–12), 20 patients who had severe TBI (GCS, 3–8), and 50 healthy controls. All patients were tested at least 6 months after injury; mean duration between injury and assessment was 1 year in patients with moderate TBI and 2 years in those with severe TBI. The subjects were given a battery of neuropsychologic tests, including IQ, motor, memory, attention, and fluency measures. Although the moderate-TBI group performed worse on all measures than the healthy control group, differences were significant only on the fluency measures. In contrast, the severe-TBI group was significantly different from the healthy controls on almost all measures. The severe-TBI group performed significantly worse than the moderate-TBI group in IQ, attention, and fluency measures.

Zec et al. (2001) compared long-term memory impairment in 32 severe-TBI patients living independently or in an intermediate-care facility at least 2 years after injury, 15 spinal-cord–injury patients, and 27 uninjured controls. The TBI patients were in coma or had altered consciousness for at least 3 days. Of the TBI patients, 25 (78%) had either hemiplegia (15) or quadriplegia (10), 59% (19) had premorbid histories of at least mild alcohol or drug use, and eight (25%) were intoxicated or under the influence of drugs at the time of injury. Spinal-cord–injury patients were recruited from the same facilities as the TBI patients, had sustained a severe spinal-cord injury, and were at least 2 years after injury. Of that group, 13 (87%) were quadriplegic, and two (13%) were paraplegic. The 27 healthy controls were matched for premorbid socioeconomic background and had no statistically significant differences in age and education from the other groups. A comprehensive neuropsychologic battery was administered to

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assess intelligence, achievement, general cognitive functioning, and memory. The TBI group scored significantly worse than the spinal-cord–injury and control groups on almost all the tests.

Bate et al. (2001) studied 35 consecutive patients admitted into an outpatient rehabilitation center over a 3-year period to identify discrete deficits of attention. All patients had severe TBI as defined by a GCS under 8 or PTA over 24 hours. Thirty-five controls were matched on age, premorbid IQ, and education. Participants and controls were given an attention test and an auditory language task. The TBI participants' reaction times were significantly longer than those of the controls, but TBI participants and controls oriented their visual attention in a similar manner. TBI participants made significantly more errors on the auditory language task than controls when they were performing under dual-task conditions; this suggested a deficit in auditory-verbal attention.

Incoccia et al. (2004) studied reaction time in 18 people who had severe TBI (GCS, under 8 for at least 6 hours), a mean interval since injury of 39 months (SD, 38 months), and an average coma duration of 20 days (SD, 12.8 days); their mean age was 32 years (SD, 12.6 years). All TBI participants had good motor recovery as evaluated clinically and had good recovery on the Glasgow Outcome Scale. The controls were 36 people who were closely matched in age and schooling. Simple visual stimuli (alertness condition) and the go-no-go tests (which require response inhibition under particular conditions) were administered. In the test with simple visual stimuli, the TBI group and the controls performed similarly; in the go-no-go tests, the TBI group performed more slowly. The authors noted that the finding indicate that people with TBI show deficits in motor programming despite good motor recovery as evaluated clinically.

Studies of Varied Severity: Mild, Moderate, or Severe Traumatic Brain Injury

Novack et al. (2000) prospectively examined 72 patients who had TBI to assess cognitive and functional recovery. Inclusion criteria involved loss of consciousness (any duration), skull fracture, PTA (any duration), and objective neurologic findings. Most subjects (49, 68%) sustained a severe TBI (GCS no higher than 8). Subjects were evaluated at 6 and 12 months after injury with a battery of neuropsychologic tests to assess orientation, speed of information processing, concentration, memory, constructional abilities, and verbal skills. Test scores were transformed to standard scores by using norms that account for age and education effects, if available. Change in performance from 6 to 12 months after injury was analyzed. Although participants with severe TBI continued to perform worse than participants with mild to moderate TBI, both groups recovered at a similar rate.

Summary and Conclusions

The committee reviewed six primary studies and 17 secondary studies. Primary and secondary studies are consistent in demonstrating sufficient evidence of an association between severe brain injury and neurocognitive deficit. Neurocognitive impairments result in a host of difficulties in people who sustain severe TBI, ranging from attention, memory, information-processing speed, and executive functions to even more robust functions, such as language and visual-spatial constructional skills. Such deficits are likely to affect psychosocial outcomes, such as the ability to drive, return to work, and adjust successfully to societal demands (see Chapter 9).

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However, there is limited/suggestive evidence that moderate TBI is associated with neurocognitive deficits. Assessment of outcomes in moderate TBI is complicated by the use of many criteria for categorizing "mild", "moderate", and "severe" injuries. Thus, in some studies, persons with "moderate" injuries had significantly greater indications of injury (more similar to other categorizations of "severe" injuries), whereas in other studies, persons with "moderate" injuries had significantly smaller indications of injury (more similar to other categorizations of "mild" injuries). The lack of consensus about what constitutes a "moderate" injury complicates understanding of the effects of such injuries.

There is inadequate and insufficient evidence of association between mild TBI and neurocognitive deficits more than 6 months after injury. Although there are known to be subjective neurocognitive complaints in some persons with mild TBI after 6 months, the studies show inconsistent results with regard to objective measures of neurocognitive performance in this group.

The committee concludes, on the basis of its evaluation, that there is sufficient evidence of an association between severe TBI and neurocognitive deficits.

The committee concludes, on the basis of its evaluation, that there is limited/suggestive evidence of an association between moderate TBI and neurocognitive deficits.

The committee concludes, on the basis of its evaluation, that there is inadequate/insufficient evidence to determine whether an association exists between mild TBI and neurocognitive deficits.

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TABLE 6.2 Closed Head Injury and Neurocognitive Outcomes

Reference	Study Design	Population	Type of TBI: Mild, Moderate, Severe; Blunt, Penetrating, Blast	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
Dikmen et al., 1995	Prospective cohort	436 adults, head-injured patients recruited at time of injury in one of three prospective longitudinal studies: behavioral outcome of head injury, patient characteristics and head-injury outcome, Dilantin prophylaxis of posttraumatic seizures 121 general TCs enrolled as part of patient-characteristics study	Minimal severity criteria: any period of LOC, PTA for at least 1 h, or other objective evidence of head trauma Head-injury severity assessed with GCS, number of nonreactive pupils, mass lesions requiring craniotomy, TFC Coma from <1 h to more than 4 weeks	Subjects assessed 1 mo, 1 year after injury Neuropsychologic tests included Halstead Reitan Neuropsycho-logical Test Battery; motor function assessed with finger-tapping, name-writing for dominant, nondominant hands; attention, concentration, flexibility, quickness measured with Seashore Rhythm Test, TMT A and TMT B, Stroop Color and Word Test Parts 1 and 2; memory evaluated with WMS, WMS-LM, WMS-VR, SR; verbal skills measured with WAIS VIQ;	At 1 year after injury: head-injured significantly worse than controls ($p < 0.01$) on neuropsychologic tests except difference on Category Test ($p < 0.05$) Nonsignificant differences on two memory measures. Severely head-injured (TFC 29 days or greater) had significant impairments on all measures ($p < 0.001$) except WMS-LM ($p < 0.01$), WMS-VR ($p < 0.05$) Clear dose–response relationship between length of coma (TFC), level of performance on	Controls matched on age, sex, education Results represent weighted averages that adjust for differences between studies in inclusion criteria	Study subjects included 85% of 514 subjects recruited from three longitudinal studies

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Reference	Study Design	Population	Type of TBI: Mild, Moderate, Severe; Blunt, Penetrating, Blast	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
				performance skills measured with WAIS PIQ, Tactual Performance Test; reasoning measured with Category Test; overall performance measured with Halstead Impairment Index	neuropsychologic measures; for example, median II for TC = 0.1; TFC < 1 h = 0.1, 1–24 h = 0.3, 25 h–6 days = 0.4, 7–13 days = 0.4, 14–28 days = 0.7, ≥29 days = 1.0		
Dikmen, 1986	Prospective cohort	20 hospitalized subjects with mild head injury; 19 uninjured friend controls 19 of 20 seen at 1 year	Mild; subjects met following criteria: coma not over 1 h or, if no coma, PTA of at least 1 h; GCS ≥12 on admission; no clinical evidence of cortical or brainstem contusion	Motor, psychomotor skills (finger-tapping speed); attention, flexibility, quickness (Speech Sounds Perception, Seashore Rhythm, TMT A, TMT B); memory and learning (WMS, SR); reasoning (Category Test); health status in terms of sickness (Sickness Impact Profile); symptoms	1 mo after TBI, mild neuropsychologic effects found, none significantly different; at 1 year after TBI, similar post-TBI symptoms reported in TBI, non-TBI subjects	Matched on age, education, sex	Exclusion criteria: subjects with prior head injury, alcoholism, cerebral disease, mental retardation, significant psychiatric disorder 15–60 years old Healthy friend controls may not control for general effects of trauma Small sample

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Reference	Study Design	Population	Type of TBI: Mild, Moderate, Severe; Blunt, Penetrating, Blast	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
				frequently reported as part of TBI (Head Injury Symptom Checklist); resumption of major activities, including work, school, homemaking (Function Status Index)			
Dikmen, 1987	Prospective cohort	102 people with closed head injury admitted into Harborview Medical Center, Seattle; 102 friend controls 97 of 102 head-injured, 88 of 102 controls evaluated at 1 year after injury	Mild, moderate, severe Subjects met following criteria: LOC or PTA over 1 h or evidence of cerebral trauma 30% GCS 3-8, 12% GCS 9-11, 59% GCS >12 23% PTA < 24 h, 25% PTA 1–6 days, 20% PTA 7–13 days, 32% PTA >14 days 77% moving-	Memory (WMS, SRP)	At 1 mo after TBI, head-injured group performed significantly worse on both memory tests ($p < 0.001$); at 1 year after TBI, most subscales still show significant impairment Memory performance a function of head-injury severity, length of coma at 1 mo; weaker relationship at 1 year after TBI	Matched on age, education, race, sex	Exclusion criteria: prior CNS injury, significant neuropsychiatric difficulties 15–60 years old

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Reference	Study Design	Population	Type of TBI: Mild, Moderate, Severe; Blunt, Penetrating, Blast	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
			vehicle accidents, 10% falls, 8% fights or assaults, 5% other				
Tate et al., 1991	Cohort	Consecutive series of first 100 admissions into adult head-injury rehabilitation unit Followed average of 6.3 years after trauma Eligible: 66 males, 21 females, sibling controls	Severe, blunt TBI: sustained open head injury, initial closed head injury later required neurosurgery Head-injured group sustained severe injuries: 98% had PTA over 1 week, 74% over 1 mo	Subjects examined by trained clinical neuropsychologist Neuropsychologic impairment evaluated with MMS, Incomplete Letters, ideomotor praxis tasks, ROCF, WAIS-R Digit Span and Vocabulary subtests, Schonell Reading Test, TMT, SR, AM, Corsi test of recency memory, WCST, TT, Word Fluency Test of Thurstone and Thurstone, DF, BCT	70% of head-injured showed impairments: 56.5% of head-injured had disorders of learning, memory vs 5% in sibling control group; 16.5% of head-injured had disturbances in basic neurocognitive skills vs 2.5% in sibling control group; 34.1% of head-injured had slowness in information processing vs 2.5% in sibling control group; 40% of head-injured had posttraumatic personality change vs 7.5% in sibling control group	Controls matched on age, sex, education, SES	Australian rehabilitation population 82 of 100 subjects completed neuropsychologic tests 15–45 years old Crude ORs

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Reference	Study Design	Population	Type of TBI: Mild, Moderate, Severe; Blunt, Penetrating, Blast	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
Lannoo et al., 1998	Cohort	85 patients consecutively admitted into the ICU of University Hospital of Gent in September 1993–February 1996 32 TCs (traumatic injuries of parts of body other than head) admitted into ICU during same study period	Moderate to severe TBI (GCS score 3–12)	Administered neuropsychologic test battery at 6 mo after injury, including tests of: attention, information processing; visual reaction time; memory, learning; verbal fluency; mental flexibility	MANOVA on neuropsychologic test battery indicated significant difference between groups ($p < 0.05$); univariate analyses showed significant differences ($p < 0.05$) on almost all tests, with TBI group performing worst		Inclusion criteria for patients and controls: ages 15–65 years, no history of CNS disease or mental retardation
Heitger et al., 2006	Prospective cohort	37 patients with mild head injury, 37 controls; patients recruited from ED of Christchurch Hospital, New Zealand; controls recruited from database of interested students	Mild	Neurocognitive testing: PASAT, TMT A and TMT B, WASI	At 12 mo, no neurocognitive deficits remained Marginal group differences on CVLT total standard score	Controls matched on age, sex, education	Exclusion criteria included alcohol or drug use; CNS disorder; psychiatric conditions; structural brain damage or hematoma on CT scan; oculomotor or somatomotor deficits; strabismus, poor visual acuity, skull fracture, or history of prior TBI

NOTE: AM = Austin Maze, BCT = Booklet Category Test, CNS = central nervous system, CT = computed tomography, CVLT = California Verbal Learning Test, DF = Design Fluency Test, ED = emergency department, GCS = Glasgow Coma Scale, ICU = intensive care unit, LOC = loss of consciousness, MANOVA = multivariate analysis of variance, MMS = Mini Mental Status, OR = odds ratio, PASAT = Paced Auditory Serial Addition Test, PIQ = performance intelligence quotient, PTA = posttraumatic amnesia, ROCF = Rey-Osterrieth Complex Figure Test, SES = socioeconomic status, SR = Selective Reminding Test, SRP = Selective Reminding Procedure, TBI = traumatic brain injury, TC = trauma control, TFC = time to follow commands, TMT A and

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TMT B = Trail Making Test A and B, TT = Tower of London Test, VIQ = Verbal Intelligence Quotient, WAIS = Wechsler Adult Intelligence Scale, WAIS-R = Wechsler Adult Intelligence Scale—Revised, WASI = Wechsler Abbreviated Scale of Intelligence, WCST = Wisconsin Card Sorting Test, WMS = Wechsler Memory Scale, WMS-LM = Wechsler Memory Scale, Logical Memory, WMS-VR = Wechsler Memory Scale-Visual Reproduction

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7

NEUROLOGIC OUTCOMES

This chapter discusses neurologic outcomes, such as seizure disorders, postconcussion symptoms, ocular and visual motor degeneration, neuroendocrine disorders, and the neurodegenerative diseases dementia of the Alzheimer's type, dementia pugilistica, parkinsonism, multiple sclerosis, and amyotrophic lateral sclerosis.

SEIZURE DISORDERS

The onset of seizures has been linked to an excessive electric discharge in the brain, cortical disruption, scarring, irritability, and the release of various endogenous neurotoxins (Silver et al., 2005). Seizures can cause a wide variety of symptoms, including loss of consciousness, shaking, and changes in vision, hearing, taste, mood, and mental function. There are two main types of seizures: generalized and focal. Generalized seizures result from abnormal electric activity on both sides of the brain, and focal, or partial, seizures result from localized excessive electric activity in one portion of the brain.

A number of studies have noted the presence of seizures after traumatic brain injury (TBI). Seizures that occur within the first 7 days after TBI are termed acute symptomatic or provoked. Seizures that occur more than 7 days after injury are termed remote symptomatic or unprovoked. If unprovoked posttraumatic seizures are recurrent, they are called posttraumatic epilepsy. A 5% incidence of posttraumatic seizures has been found after closed head injury and a 30–50% incidence after open head injury (Silver et al., 2005).

The overall risk of seizures caused by penetrating TBI related to war injuries is as high as 53%; in civilian populations, the overall risk of seizures after closed head trauma of any severity ranges from 0.5% to 8% (Salazar et al., 1985; Jennett, 1975). The prevalence of epilepsy in the general population as estimated by the Centers for Disease Control and Prevention during the period 1986–1990 was 4.7 cases per 1,000 persons (CDC, 1994). Garga and Lowenstein (2006) note that TBI "accounts for 20% of symptomatic epilepsy in the general population and 5% of all epilepsy."

Primary Studies

The committee identified 10 primary studies that examined the association of TBI with seizures: six studies of military populations with penetrating head injuries and four of civilian cohorts with closed head injuries. See Table 7-1 for a summary of the primary studies.

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The six primary studies lack the controls that were a key part of the Rochester Epidemiology Project (discussed below), but the rate of seizures in this group was generally higher than the rate in the general population. Furthermore, in most studies it is not possible to determine how many subjects had only a single seizure within 6 months of injury and none later. Thus, the overall proportion of those classified as having post-TBI seizures, ostensibly lasting more than 6 months, might be slightly inflated.

In general, the risk of unprovoked seizures after penetrating TBI is higher than the risk after even the most severe forms of closed TBI. Caveness et al. (1962) compared the number of seizures reported by others in soldiers who sustained both penetrating and nonpenetrating head injuries during World War I (WWI; Credner, 1930; Ascroft, 1941), World War II (WWII; Russell, 1951; Walker, 1961), and the Korean War (Caveness and Liss, 1961). They found that seizures were more likely to occur after penetrating head injury (34–43%) than after blunt and blast head injury (12–24%). Of the 317 cases in the WWI cohort, 34.8% reported having seizures compared with 28% of those in the WWII cohort and 24.1% of those in the Korean War cohort. The proportion of patients who had penetrating TBI that later had seizures ranged from 42% in the Korean War cohort (Caveness and Liss, 1961) to 47% in the WWI cohort (Ascroft, 1941).

A followup study was conducted by Caveness (1963) 8–11 years after initial injury. During the followup period, 356 of the original Korean War subjects participated (76.2% of the total and 87.2% of those suitable for followup). Information was collected through mailed questionnaires, physical examinations, interviews with the American Red Cross, and a review of Veterans Administration records. During the period 1957–1958, additional VA information was available on 84.6% of the participants. Questionnaires were obtained in 1961–1962 from 90.5% of the participants, personal letters from 21.6%, and telephone replies from 9.6% (Caveness, 1963). Caveness (1963) found that of the 356 men, 109 (30.6%) had postinjury seizures; 30 patients had seizures that did not persist beyond 6 months, so 79 (22%) apparently had seizures more than 6 months after injury. Of those with penetrating head wounds, 42% suffered seizures, and 16.4% of those with blunt head wounds had seizures. The authors noted that there was no significant difference in the number of seizures between the total original group and those who were followed for 8–11 years.

Evans (1962) assessed the prevalence of seizures in the same 422 head-injured Korean War veterans at 3–11 years after injury. The overall prevalence was 19.7%. The prevalence was 32% in those with penetrating head injuries, 2% in those with blast wounds, and 8% in those with blunt head injuries.

Phillips (1954) conducted a conditional cohort study of 500 head-injured men admitted within 3 days of injury into the Military Hospital for Head Injuries, Oxford. Information was collected on amnesia, electroencephalographic findings, personal and family history, cerebrospinal fluid (CSF) pressure, epilepsy, intracranial hemorrhage, CSF leak, infection, mental-health changes, condition on discharge, and followup after rehabilitation. The author found that 31 men (6%) developed seizures after injury; 24 had generalized seizures, five focal seizures, and two mixed seizures. Seven with seizures had focal signs after injury, of whom five had focal seizures and two had generalized seizures. All the focal seizures occurred within the first 6 days after injury, whereas generalized seizures typically did not typically for several months. It is unclear whether the head injuries were combat-related, and the time between injury and seizure is ambiguous. Thus, it was not possible to determine from the report the number of patients who had their only seizure within 6 months of injury.

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Russell (1968) conducted a conditional cohort study of the prevalence of epilepsy after penetrating head injury in 185 patients injured in WWII. The men were followed for 10–20 years after injury. Of the 185, 77 (41.6%) had posttraumatic grand mal epilepsy, and 40 (21.6%) were still having seizures 10 years or more after injury. The study was limited in that it did not include a control population and the cohort was not described in terms of age, sex, and nationality. It also is not clear who may have had only one seizure in the first 6 months after injury.

Weiss et al. (1983) studied 1,221 head-injured Vietnam veterans enrolled in the Vietnam Head Injury Study (VHIS). Although the focus of the study was on prognostic factors in the occurrence of epilepsy, they reported that 31% of the cohort had seizures more than a week after injury. A followup study of this cohort was reported by Salazar et al. (1985) and by Rish et al. (1983).

The four studies of closed TBI and seizure risk in civilians come from the Rochester Epidemiology Project (see Chapter 5). Annegers et al. (1980) reported the risk of unprovoked seizures in a cohort of 2,747 patients (1,132 children and 1,615 adults) in Olmsted County, MN, who had sustained TBI in 1935–1974. An additional 4,541 patients who sustained TBI in 1975–1984 were added later (Annegers et al., 1998). As part of the Rochester Epidemiology Project, medical records containing physician diagnoses of TBI were linked to later medical records documenting unprovoked seizures in the study interval and compared with records of those who did not sustain TBI. The authors found the overall risk of unprovoked seizures after TBI to be 3.6 times (95% CI, 2.7–4.8) that in the noninjured population. That risk, also known as the standardized incidence ratio (SIR), was highest among those with severe TBI (SIR, 17.0; 95% CI, 12.3–23.6), followed by those with moderate TBI (SIR, 2.9; 95% CI, 1.9–4.1) and mild TBI resulting in loss of consciousness (LOC) or posttraumatic amnesia (PTA; SIR, 1.5; 95% CI, 1.0–2.2). The overall unprovoked-seizure risk was found to be highest in the first year after injury (SIR, 12.7) and to fall (to 4.4) 1–4 years after injury and fall further (to 1.4) 5 years or more after injury. That pattern of seizure risk over time was also found in each TBI-severity group. Although the risk of unprovoked seizures after mild TBI was increased at all times after injury, it was significantly different from the risk in the uninjured population only during in the period 1–4 years after injury.

A limitation of both Annegers et al. studies (1980, 1998) is that the authors included children in the study and in the risk estimates. It is not possible with the available data to calculate rates for adults only, and reported rates may be misleading inasmuch as seizures occur more frequently in children than adults. Therefore, the generalizability to the veteran population is unclear.

Two additional published analyses of the Rochester Epidemiology Project included children but presented the post-TBI incidence of seizures in adults separately. Annegers and colleagues (1995) reported that the age-adjusted incidence of post-TBI seizures in adults ranged from 2.0/100,000 person-years in 25- to 34-year-olds to 14.0/100,000 person-years in those over 74 years old. In addition, the age-adjusted incidence of post-TBI seizures was higher in males at all ages (8.6/100,000 person-years in males and 4.8/100,000 person-years in females). Singer (2001) used data from the Rochester Epidemiology Project to compare the incidence of post-TBI seizures with the incidence of idiopathic epilepsy previously determined for Olmsted County. Singer et al. (2001) found that the incidence was highest in the first year after head injury. Compared with the expected seizure rate in idiopathic epilepsy, seizures were 3.1 times more likely to occur during the first year after mild head injury, 6.7 times more likely after moderate

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head injury, and 95 times more likely after severe head injury. Overall, mild head injury resulted in 0.4 excess seizure per 1,000 per year, whereas severe head injury resulted in 10 per 1,000 per year.

Secondary Studies

The committee identified 19 secondary studies of the relationship between TBI and the onset of seizures. The major limitation of the studies is lack of a control or comparison population.

Two secondary studies were drawn from the VHIS registry, which is described in more detail in Chapter 5. Both studies found an increase in epilepsy 15 years after injury. Rish and colleagues (1983) studied male Vietnam veterans who had had penetrating craniocerebral injuries and had survived for 1 week after injury. Of 1,127 veterans, 378 had a diagnosis of posttraumatic epilepsy (34%). Similarly, Salazar and colleagues (1985) studied the first 421 head-injured veterans to followup as part of phase II of the VHIS and found that 53% had posttraumatic epilepsy. The relative risk of epilepsy in the head-injured veterans was 580 times that in the general age-matched population in the first 6 months and fell to 25 times higher after 10 years. About 57% of patients with seizures had attacks within a year after injury; in about 18%, the first seizure occurred more than 5 years after injury; and in 7%, the first seizure came 10 years or more after injury. At 15 years after injury, 28% of all those who sustained head injuries had persistent seizures.

Jennett and Lewin (1960) and Jennett (1962, 1969, 1973, 1975) conducted a number of studies of posttraumatic epilepsy in head-injured patients admitted into hospitals in Oxford, Glasgow, and Rotterdam. (A detailed description of the cohort is included in Chapter 5.) Jennett and Lewin (1960) studied 1,000 patients who sustained nonmissile head injuries and were consecutively admitted to the Radcliffe Infirmary, Oxford, in 1948–1952. In the first month after injury, 4.6% of the cohort experienced seizures. Four years after the last case was admitted, the authors followed up the series to determine the rate of seizures and found that 28 (10%) of the 275 patients who were able to be followed had one or more seizures. Jennett (1962) assessed the incidence of epilepsy in 315 patients of the above cohort. The 315 patients included 75 who were in the inclusive series with early epilepsy and 240 from the original 1,000 who did not have early epilepsy. Some 58 cases of late epilepsy were observed in this population. Jennett (1969) expanded on the original Oxford series of patients by including additional cases and cases from a hospital in Glasgow, Scotland. Seizure risk was assessed in 600 patients who had blunt head injury and depressed skull fracture. After 1 year, 9.5% of the 333 patients able to be followed up had developed seizures.

Jennett (1973) studied the Oxford and Glasgow population and included an additional 250 head-injured patients from Rotterdam who had depressed fractures. The incidence of late epilepsy in the unselected series of injuries was calculated to be about 5% and about 45% in those who sustained missile injuries. Jennett (1975) provided a summary of the seizure cases identified in the Oxford, Glasgow, and Rotterdam cohorts.

Several other authors reported on head-injured patients admitted into the Radcliff Infirmary. Roberts (1979) studied the subset of head-injured patients admitted with severe TBI (PTA of over a week or LOC of over a month). Of the 291 patients in this series examined 10–24 years after head injury, 25.5% developed seizures (Roberts, 1979). Lewin et al. (1979) reported

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that posttraumatic epilepsy was diagnosed in 28% of 479 patients admitted into the John Radcliffe Infirmary in Oxford in 1955–1969 with a head injury resulting in PTA or LOC of a week or more.

Three secondary studies assessed seizure rates in veterans or military personnel who had sustained penetrating head injury. Wagstaffe (1928) studied the prevalence of epilepsy in 377 WWI veterans who had sustained a penetrating gunshot wound of the head and found that 37 had seizures and that "traumatic epilepsy is nearly ten times more common with penetrating wounds of the dura than with other injuries to the head." Watson (1947) studied the prevalence of epilepsy in 279 patients admitted with penetrating head injury sustained during WWII and found that 101 (36.2%) had had seizures at the 2-year followup. Russell and Davies-Jones (1969) conducted a conditional cohort study of the occurrence of epilepsy after penetrating head injury in WWII soldiers and found that 42% of 562 soldiers had had epilepsy by 5 years after the penetrating TBI.

Four secondary studies assessed seizure rates in head-injured patients admitted into hospitals. Miller and Jennett (1968) studied seizure rates in 400 patients who had penetrating or puncture head wounds. Over half had brief or no LOC and PTA less than 1 hour, and late posttraumatic epilepsy occurred in 9.5%. Stevenson (1931) assessed the occurrence of epilepsy in 84 patients who sustained gunshot wounds of the head; 74% of those with penetrating and 23% of those with superficial wounds of the head had epilepsy. Sargent (1921) found that 800 of 18,000 people who had sustained gunshot wounds of the head had seizures (4.5%). And Penfield and Shaver (1945) assessed epilepsy in patients admitted into a hospital because of a head injury in 1929–1941; of the 407 patients assessed, 11 developed epilepsy, for an incidence of 2.7%.

Two secondary studies assessed risk factors for posttraumatic epilepsy. Angeleri et al. (1999) conducted a prospective study of risk factors for posttraumatic epilepsy in 137 consecutively enrolled patients up to 1 year after injury. They found that the posttraumatic epilepsy group included 18 who had at least two seizures at 2-12 months; risk factors included a low score on the Glasgow Coma Scale (GCS), early seizures, and single brain lesions seen with computed tomography (CT).

Englander et al. (2003) also studied risk factors for late posttraumatic epilepsy in 647 patients who had moderate or severe TBI and were admitted into trauma centers within 24 hours of injury. The patients were followed for up to 2 years, until death, or until their first late posttraumatic seizure. Sixty-six had late posttraumatic seizures, 337 had no late posttraumatic seizures during the full 24-month followup, 167 had no late posttraumatic seizures during the time they were followed, and 54 patients were given anticonvulsants and did not have late posttraumatic seizures. The authors found that the highest cumulative probabilities of late posttraumatic seizures were associated with biparietal contusions (66%), dural penetration with bone and metal fragments (62.5%), multiple intracranial operations (36.5%), multiple subcortical contusions (33.4%), subdural hematoma with evacuation (27.8%), midline shift greater than 5 mm (25.8%), and multiple or bilateral cortical contusions (25%). In addition, initial GCS score was associated with the cumulative probabilities of late posttraumatic seizures at the 24-month followup (GCS score of 3–8, 16.8%; score of 9–12, 24.3%; and score of 13–15, 8.0%).

Finally, Ryan et al. (2006) assessed seizure symptoms in 127 college undergraduates who reported a history of head injury. Participants were divided into three categories on the basis of their self-reported head-injury status: students who sustained head injury with brief LOC,

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students who had head injury with brief alteration of consciousness (AOC), and students who had no head injury. The authors found that those in the LOC group reported a greater frequency of seizure symptoms and a greater number of clinically significant seizure symptoms ($p < 0.015$) than the no–head-injury group and had more clinically significant seizure symptoms than the AOC group ($p < 0.09$). There was no significant difference between the AOC and no–head-injury groups in frequency of seizure symptoms or number of clinically significant seizure symptoms.

Summary and Conclusion

The committee reviewed 10 primary studies and 19 secondary studies of TBI and seizures. The secondary studies are largely supportive of the primary studies that indicate that brain injury is associated with seizure activity. Unprovoked seizures were strongly associated with most types of TBI. The highest risk of unprovoked seizures occurred in those suffering penetrating head injury (which usually occurred during military combat): 32–53% had seizures. After blunt trauma, seizure risk varied with initial injury severity. Compared with the healthy, uninjured population, the risk of unprovoked seizures was about 17–95 times higher after severe TBI and 2.9–6.6 times higher after moderate TBI. The seizure risk after mild TBI that resulted in LOC or PTA was about 1.5 times that in the healthy, uninjured population. The risk of seizure after a blast is not clear, although one study of Korean War veterans reported that 2% suffered a seizure within 11 years of injury. In general, the seizure risk after all forms of TBI appears to be highest within the first year after trauma and to decline thereafter.

Animal models confirm the presence of seizures after both penetrating and blunt TBI. Using a lateral fluid percussion model of TBI in adult rats, several authors have demonstrated both provoked and unprovoked seizures (Golarai et al., 2001; Santhakumar et al., 2001; D'Ambrosio et al., 2004; Kharatishvili et al., 2006). A single episode of severe fluid percussion injury can cause a spontaneous seizure and recurrent seizures that become chronic and become worse with time (D'Ambrosio et al., 2004). Seizures have also been demonstrated after TBI induced in rats in a penetrating–ballistic-injury model (Williams et al., 2005).

The committee concludes, on the basis of its evaluation, that there is sufficient evidence of a causal relationship between sustaining a penetrating TBI and the development of unprovoked seizures.

The committee concludes, on the basis of its evaluation, that there is sufficient evidence of a causal relationship between sustaining a severe TBI and the development of unprovoked seizures.

The committee concludes, on the basis of its evaluation, that there is sufficient evidence of a causal relationship between sustaining a moderate TBI and the development of unprovoked seizures.

The committee concludes, on the basis of its evaluation, that there is limited/suggestive evidence of an association between sustaining a mild TBI resulting in loss of consciousness or amnesia and the development of unprovoked seizures.

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T**ABLE 7.1** Seizure Disorders and TBI

Reference	Study Design	Population	Type of TBI: Mild, Moderate, Severe; Blunt, Penetrating, Blast	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
Annegers et al., 1980	Retrospective cohort	2,747 patients of Olmsted County, MN, with head injuries sustained 1935–1974 compared with age-, sex-specific rates in general population; followed for 28,176 person-years Excluded deaths within 1 mo, seizures before TBI, prior epilepsy, second head injury, prior TBI, seizure within 1 week of TBI, febrile seizures 1,132 of 2,747 patients (41%) were children less than 15 years old.	TBI determined by health-care provider, documented in medical record 195 severe head injuries: documented brain contusion (diagnosed by observation during surgery,or from focal neurologic abnormalities), intracranial hematoma, or at least 24 h of unconsciousness or PTA 912 moderate head injuries: skull fractures or head injuries, causing at least 0.5 h of unconsciousness or PTA 1,640 mild head injuries: no fracture but unconsciousness	Seizures determined from medical records	SIR; seizures in adults, children: <1 year after trauma, SIR, 12.7 (95% CI, 7.7–20); 1–4 years after trauma, SIR, 4.4 (95% CI, 2.7–6.9); 5+ years after trauma, RR, 1.4 (95% CI, 0.7–2.5); overall SIR, 3.6 (95% CI, 2.7–4.8)	Age- and sex-matched controls	Children included in risk estimate; results include children, whose rates of seizures may be different from adults' rates

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Reference	Study Design	Population	Type of TBI: Mild, Moderate, Severe; Blunt, Penetrating, Blast	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
			or PTA for less than 30 min				
Annegers et al., 1998	Retrospective cohort	Same as above, but new cases added (4,541) for additional 10-year period (1975–1984) and followup of original cases (followup of 53,222 person-years)	Mild: LOC or amnesia for less than 30 min Moderate: LOC for 30 min–24 h or skull fracture Severe: LOC or amnesia for more than 24 h, subdural hematoma, or brain contusion	Seizures determined from medical records	Including children, adults: Mild: SIR, 1.5 (95% CI, 1.0–2.2); moderate, SIR, 2.9 (95% CI, 1.9–4.1); severe, SIR, 17.0 (95% CI, 12.3–23.6) Mild: <1 year, SIR, 3.1 (95% CI, 1.0–7.2); 1–4 years, SIR, 2.1 (95% CI, 1.1–3.8); 5–9 years, SIR, 0.9 (95% CI, 0.3–2.6); ≥10 years, SIR, 1.1 (95% CI, 0.5–2.1) Moderate: <1 year, SIR, 6.7 (95% CI, 2.4–14.1); 1–4 years, SIR, 3.1 (95% CI, 1.4–6.0); 5–9 years, SIR, 3.0 (95% CI, 1.2–6.2); ≥10 years, SIR, 1.8 (95% CI, 0.8–3.6) Severe: <1 year, SIR, 95.0 (95% CI, 58.4–151.2); 1–4 years, SIR, 16.7 (95% CI, 8.4–32.0); 5–9 years,	Cumulative probability of unprovoked seizure after TBI estimated with Kaplan-Meier method Importance of prognostic factors determined with Cox proportional hazards analysis	Children included in risk estimate; results include children, whose rates of seizures may be different from adults' rates

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Reference	Study Design	Population	Type of TBI: Mild, Moderate, Severe; Blunt, Penetrating, Blast	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
					SIR, 12.0 (95% CI, 4.5–26.6); ≥10 years, SIR, 4.0 (95% CI, 1.1–10.2)		
Singer, 2001	Retrospective cohort	Same population as above (4,541 patients) with TBI diagnosed in Olmsted County, MN, 1935–1984. Post-TBI seizure incidence rates compared with expected idiopathic seizure rate as ratio (comparative incidence rate) and absolute difference (excess event rate) per 1,000 of population per year	Mild head injury: LOC or amnesia for less than 30 min Moderate head injury: LOC for 30 min–24 h or skull fracture Severe head injury: LOC or amnesia for more than 24 h, subdural hematoma, or brain contusion	Seizures determined from medical records	97 of 4,541 TBI cases had at least one seizure in 50-year period Mild head injury: comparative incidence rate, 1.52 (3.1 in first PT year, 2.1 in years 1–5); excess event rate, 0.3 Moderate head injury: comparative incidence rate, 2.85 (6.65 in first PT year, 3.1 in years 1–5); excess event rate, 1.1 Severe head injury: comparative incidence rate, 17.0 (95 in first PT year, 16.7 in years 1–5); excess event rate, 10		Included children and adults
Annegers et al., 1995	Retrospective cohort	692 patients in Olmsted County, MN, who developed acute symptomatic post-TBI seizures in	Head trauma	Seizures determined from medical records; acute symptomatic seizures defined as occurring	Age-adjusted incidence rates of acute symptomatic post-TBI seizures, 2.0 per 100,000 person-years (25- to 34-year-olds) to 14.0	Age	Included children and adults

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Reference	Study Design	Population	Type of TBI: Mild, Moderate, Severe; Blunt, Penetrating, Blast	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
		1955–1984		within 7 days of brain trauma or during period of recovery from such an insult	per 100,000 person-years (>74-year-olds); incidence higher in males than females at all ages (overall age-adjusted rate, 8.6 in males vs 4.8 in females)		
Caveness et al., 1962	Five retrospective cohorts from WWI, WWII, Korean War	WWI: 1,990 German war injuries; head trauma examined 1914–1928 (>50% were >5 years after trauma)	Blunt and penetrating	Seizures determined at Hechsler Institution	38.2% had seizures	None	No referent group; undetermined whether there were preinjury seizures; inability to determine number who may have had their one and only seizure within first 6 mo after TBI
		WWI: 317 GSW of head, 7–20 years after trauma	Penetrating	Seizures determined at British Ministry of Pensions	34%		
		WWII: 820 GSWs within 5 years after trauma;	Dural penetration	Seizure determined by postal inquiry	43%		
		WWII: 739 head injured selected from Army and VA 7–8 years after trauma	Blunt, blast, penetrating	Seizures	28% (missile, 33.9%; blunt, blast, 24.1%)		
		Korean War: 407 random sample 5 years	"Craniocerebral injury in combat"	Seizures determined by record review or	24.1% (missile, 35%; blunt, blast: 12.2%)		

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Reference	Study Design	Population	Type of TBI: Mild, Moderate, Severe; Blunt, Penetrating, Blast	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
		after trauma		interviews			
		214 missile, 52 blast, 141 blunt	135 with dura matter rupture				
Caveness, 1963	Conditional cohort	356 Korean War veterans with head injuries treated by study author or two other NS and assessed 7–8 years after injury	Penetrating (52%), blunt (48%) Six categories: I, head blow without MS change; II, transient LOC; III, focal brain injury without dural penetration; IV, dural penetration without neurologic deficit; V, dural penetration with neurologic deficit; VI, dural penetration with profound complications	Seizures determined with postal questionnaire	Prevalence of seizures: overall, 30.6%; seizures lasting >6 mo, 22%; penetrating, 42.1%; blunt, 16.4%; I, 7.1%; II, 10.4%; III, 39.0%; IV, 20.0%; V, 51.4%; VI, 57.3%		No reference group; no screening for preinjury seizure disorder Cohort may overlap with Evans 13526
Evans, 1962	Conditional cohort	422 Korean War veterans with head injuries treated at US Naval Hospital in Yokusaka or on US hospital ships, assessed	Penetrating (52%), blunt (35%), blast (12%) Five categories: I, no scalp lacerations, no skull fracture; II,	Seizures determined with postal questionnaire	Prevalence of seizures: overall, 19.7%; penetrating, 32%; blunt, 8%; blast, 2%; I, 1%; II, 1.7%; III, 1.2%; IV, 1.7%; V, 14% Seizure prevalence		No reference group; no screening for preinjury seizure disorder Cohort may overlap with Caveness 13530 Inability to determine number who may have had their one and only

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Reference	Study Design	Population	Type of TBI: Mild, Moderate, Severe; Blunt, Penetrating, Blast	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
		3–11 years after injury	scalp lacerations, no skull fracture; III, linear skull fracture; IV, depressed skull fracture; V, brain penetration		increased with increasing duration of LOC and PTA		seizure within first 6 mo after TBI
Phillips, 1954	Conditional cohort	500 adult male "military personnel" admitted into military hospital for head injuries in Oxford for head injury	Blunt head trauma	Seizures	6% had seizure		No controls; unclear whether combat-related; unclear interval between injury and seizures; inability to determine number with seizures persisting beyond 6 mo
Russell, 1968	Conditional cohort	185 patients followed >10 years after injury	Penetrating TBI	Seizures	21.6 % had seizures		No controls, but combat-related; cohort not described in terms of age, sex, nationality, how wounded; inability to determine number with seizures persisting beyond 6 mo
Weiss et al., 1983	Prospective cohort (W.F. Caveness VHIS registry)	1,221 head injured Vietnam veterans	Penetrating TBI	PT epilepsy	31% had seizures >1 week after injury; formula used to describe onset of first seizures after injury.		Inability to determine number with seizures persisting beyond 6 mo, but Salazar and Rish report that 43% of seizure patients in this cohort had their first seizure more than 1 year after injury

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NOTE: CI = confidence interval, GSW = gun shot wound, LOC = loss of consciousness, MS = mental status, NS = neurosurgeons, PT = posttrauma, PTA = posttraumatic amnesia, RR = relative risk, SIR = standardized incidence ratio, TBI = traumatic brain injury, VA = Department of Veterans Affairs, VHIS = Vietnam Head Injury Study, WWI = World War I, WWII = World War II.

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POSTCONCUSSION SYMPTOMS

Numerous symptoms have been reported after TBI. Both the International Classification of Diseases, 10th Edition (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) recognize a constellation of symptoms that may occur after TBI. The ICD-10 recognizes a postconcussion syndrome (PCS), and the DSM-IV postconcussional disorder (PCD). The ICD-10 criteria used to diagnose PCS include three or more of the following eight symptoms: headache; dizziness; fatigue; irritability; subjective concentration difficulty; memory impairment; insomnia; and reduced tolerance of stress, emotional excitement, or alcohol. There is no clear requirement that the symptoms began or worsened after the head trauma although there is a statement that the syndrome occurs after head trauma. The DSM-IV criteria include the presence of three or more of the following symptoms that occur or worsen shortly after the trauma and last at least 3 months: fatigue; disordered sleep; headache; dizziness; irritability; changes in personality; apathy or lack of spontaneity; or anxiety, depression, or affective lability (Luis et al., 2003). Criteria for PCD, which is a research definition rather than a clinical definition, also include difficulty in attention or memory on the basis of neuropsychologic testing and a finding that the symptoms cause substantial impairment in social or occupational functioning and constitute a decline from a previous level of functioning. Although there were numerous studies of persistent symptoms after TBI, none looked specifically at PCS or PCD.

Primary Studies

Eight primary studies were identified that looked at the association of TBI with symptoms. Hoge et al. (2008) looked at symptoms reported by soldiers 3–4 months after their return from year-long deployments in Iraq and compared those who reported LOC or altered mental state with those who reported an injury that did not involve an altered mental state. Two of the studies evaluated the relationship between TBI and postconcussion symptoms in separate cohorts of people with head trauma involving brief LOC who had been seen in the emergency departments (EDs) of two hospitals in Kaunas, Lithuania (Mickeviciene et al., 2002, 2004). Masson (1996) evaluated the prevalence of symptoms in patients in Aquitaine, France, 5 years after hospitalization for head injury. Stulemeijer et al. (2006a) evaluated fatigue in patients who attended the ED of a Dutch hospital. Those four studies compared the rates of symptoms in TBI patients with rates in patients who had trauma that did not involve the head. McLean (1993) assessed the rate of symptom endorsement 12 months after hospitalization for head injury compared with the rate in friends who did not experience a head injury. Heitger (2007) compared subjects who had mild TBI and were admitted into a New Zealand ED with uninjured controls recruited from a database of volunteers interested in participating in research studies. Gerber and Schraa (1995) conducted a prospective study of patients consecutively admitted into an ED because of mild TBI and compared them with a group that had orthopedic injuries and with uninjured controls. (See Table 7-5 for a summary of the primary studies of this outcome.)

Hoge et al. (2008) studied the symptoms that were bothersome or frequent in 2,525 US Army soldiers 3–4 months after their return from year-long deployments in Iraq. They compared the 124 who reported injuries involving LOC and the 260 who reported injuries with altered mental state with the 435 who reported other injuries. Symptom rates among the 1,706 who

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reported no injury were also given. Soldiers were recruited from two brigades, and 59% of them completed the questionnaire. Normal transfers to other units, training, and attendance at military schools were the main reasons for not filling out the questionnaire. Of soldiers who attended recruitment briefings, 98% agreed to participate. Soldiers were classified according to their responses about injury during deployment. One group reported losing consciousness (being knocked out); another group denoted as having altered mental state reported being dazed, confused, "seeing stars", or not remembering the injury; a third group reported an injury without altered mental state; and a fourth group reported no injury. Physical symptoms were measured by using the Patient Health Questionnaire 15-item somatic-symptom severity scale (PHQ-15). Five additional questions asked about symptoms regarded as important postconcussion symptoms that are not part of the PHQ-15. The authors tallied the number of soldiers reporting "bothered a lot" by the symptom or the number reporting "more than half the days" for fatigue, sleep disturbance, concentration problems, or irritability. Common postconcussion symptoms studied were headache, dizziness, fatigue, sleep disturbance, memory problems, balance problems, ringing in the ears, concentration problems, and irritability. All nine symptoms were reported more by those with LOC than by those with injuries that involved no alteration in consciousness (odds ratios [ORs], 1.89–3.45; each p value < 0.02). The most common problems were irritability, fatigue, and sleep disturbance, each of which was reported by over half the soldiers who had LOC. Those with altered mental state but no LOC associated with their injuries reported significantly more irritability, concentration problems, balance problems, headache, and sleep disturbance (ORs, 1.38–2.46; each p value < 0.05). The most common reported symptoms in those with altered mental state were irritability (47.6%) and sleep disturbance (44.9%) (see Table 7.2). Statistical tests comparing those who had mild TBI with those who had no injury were not presented, but the rates of symptom endorsement were lower in those without injury, and the sample was much larger.

Hoge et al. (2008) also presented ORs for posttraumatic stress disorder (PTSD) and depression. PTSD was more frequent in both groups with TBI, that is, those with LOC and altered mental status; depression was more frequent in those with LOC than in those with any other injuries. After adjusting for PTSD and depression, however, headache was the only postconcussion symptom significantly more frequently reported, and that was only in the group with LOC. That raises the question of whether postconcussion symptoms are caused by mild TBI or PTSD and depression, or both. Neither Hoge et al. (2008) nor other studies reviewed present data that allow determination of which symptoms might be caused specifically by the TBI or the PTSD and depression.

TABLE 7.2 Symptoms After Deployment According to Type of Injury During Deployment

Symptoms	Injury with LOC (n = 124), %	Injury with Altered Mental Status (n = 260), %	Other Injury (n = 435), %	No Injury (n = 1,706), %	p Value for LOC vs Other Injury	p Value for Altered Mental Status vs Other Injury
Headache	32.2	17.7	12.1	8.4	<0.001	0.04
Dizziness	8.3	5.9	3.1	1.8	0.01	0.07
Fatigue	53.2	39.7	34.6	25.2	<0.001	0.21
Sleep disturbance	53.8	44.9	37.2	24.1	0.001	0.05
Memory problems	24.6	16.2	13.7	7.4	0.005	0.38
Balance problems	8.3	6.7	2.8	1.6	0.02	0.02
Ringing in ears	23.5	17.9	14.0	5.9	0.01	0.17

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Symptoms	Injury with LOC (n = 124), %	Injury with Altered Mental Status (n = 260), %	Other Injury (n = 435), %	No Injury (n = 1,706), %	p Value for LOC vs Other Injury	p Value for Altered Mental Status vs Other Injury
Concentration problems	31.4	26.0	18.1	10.2	0.002	0.02
Irritability	56.8	47.6	36.8	24.7	<0.001	0.006

NOTE: LOC = loss of consciousness.
SOURCE: Hoge et al., 2008.

Mickeviciene et al. (2002) studied the frequency and severity of a number of postconcussion symptoms—including headache, dizziness, memory problems, concentration problems, fatigue, and irritability—in a retrospectively identified inception cohort of 200 patients seen in the ED of Kaunas University Hospital or Red Cross Hospital in Kaunas, Lithuania, for head trauma involving LOC lasting 15 minutes or less. Patients with other major injuries or LOC over 15 minutes were excluded. The control group consisted of 200 age- and sex-matched controls with minor injuries (not involving the head or neck) who reported never having had a previous concussion and who were seen in the EDs within 2 weeks of the TBI cases. Self-report questionnaires with questions about general health and a detailed section about headaches and less extensive questioning about other symptoms were mailed to participants 22–35 months after their injuries. Subjects returned the questionnaires before they were told of the interest in the relationship between TBI and symptoms. Study participants were asked about the frequency of headache, dizziness, memory problems, and concentration problems and were asked to mark a visual analogue scale to indicate the degree of 15 symptoms on a scale ranging from 0 (“no”) to 100 (“much”). Some 66% of TBI participants and 73% of controls returned the questionnaires. The two groups were similar in most demographic characteristics although participants with concussion reported slightly lower education and were less likely to be currently married. The authors found no significant differences between subjects who had sustained head injuries with brief LOC and controls in occurrence of any headaches during the previous month ($p = 0.92$) or for more than 7 days in the previous month ($p = 0.95$); comparative results were similar for headaches in the previous year. No significant differences were found between the TBI participants and controls in extent of self-reported dizziness, memory problems, or concentration problems. Of the 15 postconcussion symptoms marked on a visual analogue scale, only depression ($p = 0.002$) and alcohol intolerance ($p = 0.04$) were endorsed more by those with TBI. The investigators considered headache, memory problems, concentration problems, dizziness, fatigue, and irritability to be core postconcussion symptoms and looked at the numbers with PCS, which was defined as the number who endorsed all six core symptoms, including at least one to what the authors defined as a significant degree. There was no significant difference between those with TBI and controls in the number endorsing each symptom to a pronounced degree and the other five core symptoms to any degree (p, 0.06–0.87). Only one person with TBI and three controls endorsed all six core symptoms to a significant degree. The study was limited by the fact that no CT or magnetic resonance imaging (MRI) was done to rule out intracranial lesions, by the moderate response rates, and by the collection of data by mail questionnaires rather than in-person interviews. It has the advantage of having been conducted in a country where there is no financial incentive to overreport symptoms. In addition, the subjects were unaware of the reason for the study.

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Mickeviciene et al. (2004) conducted a prospective cohort study to investigate the relationship of posttraumatic symptoms, the influence of sociodemographic factors, and the effect of expectation on symptoms of PCS related to head injury. The study population included 300 patients seen in the ED of Kaunas University Hospital or Red Cross Hospital in Kaunas, Lithuania, for head trauma involving LOC lasting 15 minutes or less. The control group consisted of 300 sex- and age-matched people who had sustained a minor nonhead injury. Some 64% of those with TBI and 72% of controls returned the questionnaires at 1 year after injury. Subjects were given a standard self-report questionnaire with questions about postconcussion symptoms (the Rivermead Post-Concussion Symptoms Questionnaire, RPQ) and were also asked to mark a visual analogue scale to indicate the severity of symptoms on a scale ranging from 0 ("no") to 100 ("much"). The authors found that reports of any headaches after 1 year ($p = 0.98$) and frequent headaches ($p = 0.15$) did not differ significantly between the head-injured patients and the controls. The head-injured subjects more commonly reported some memory problems ($p < 0.001$), some concentration problems ($p = 0.04$), and some dizziness ($p = 0.02$). They did not differ from controls in dizziness occurring every day, constant memory problems, and constant severe concentration problems after 1 year after injury. On the visual analogue scale, the subjects with TBI reported significantly more memory problems, concentration problems, and tiredness; there was no significant difference in the other 12 symptoms. No relationship was found between headache or cognitive dysfunction at 1 year and severity of concussion. The study was limited by the fact that only 51 head-injured participants had CT imaging to rule out intracranial lesions, by the moderate response rates, and by collection of data by mail questionnaires. The subjects were sent the questionnaires soon after injury and 3 months later, and this made them aware of the possibility of persistent postconcussion symptoms. It has the advantage of having been conducted in a country where there is no financial incentive to overreport symptoms.

Heitger et al. (2007) used the RPQ to collect information on symptoms from 37 subjects presenting at the Christchurch, New Zealand, Hospital ED with mild TBI (GCS scores, 13–15 at first assessment with no consecutive scores below 13; PTA less than 24 hours; and no structural damage or skull fracture on head CT if obtained). The subjects and controls had no history of TBI with persisting symptoms, no central neurologic disorder or psychiatric disorder, and no regular intake of psychoactive drugs or history of drug abuse. Controls were recruited via a volunteer database made available by the Department of Psychology at the University of Canterbury, Christchurch, New Zealand, and were individually matched to the mild-TBI cases on age, sex, and years of formal education. The paper states the number who reported the symptom at all and the number who reported that it was at least a mild problem at 1 week and 3, 6, and 12 months after injury. All pairs participated in the 1-month and 6-month evaluation, and 31 (84%) in the 12-month evaluation. Most controls answered the questionnaire only once. At 6 months, the TBI subjects reported significantly higher scores on the 0–4 scale for each of headaches, dizziness, noise sensitivity, fatigue, irritability, feeling depressed, poor memory, poor concentration, slowed thinking, double vision, and restlessness (each $p < 0.05$) (see Table 7-3 for detailed results). At 12 months, those with mild TBI reported significantly more headaches, fatigue, poor memory, poor concentration, blurred vision, and double vision (each $p < 0.05$). There was no significant difference at either time in nausea, sleep disturbance, frustration, or light sensitivity. A strength of the study is that no patients were involved in litigation and or were seeking compensation beyond the standard provisions of the no-blame insurance that covers all New Zealand residents. A limitation is that controls were volunteers interested in participating in research and may not have been similar to the mild-TBI subjects. Most also answered the

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questionnaire only once, although responses by the 10 controls who completed the questionnaire more than once were consistent. In addition, the controls were uninjured, so the effects of mild TBI cannot be separated from the effects of injury in general.

TABLE 7.3 Frequency of Symptoms on RPCS Questionnaire

	Patients Reporting Symptoms, %				**Controls**
	6 months		**12 months**		
Symptom	Score of 2 or Higher[a]	p Value[b]	Score of 2 or Higher	p Value[b]	Score of 2 or Higher
Fatigue	22	<0.01	26	<0.05	8
Headache	22	<0.01	26	<0.05	3
Dizziness	19	<0.05	23		3
Poor concentration	27	<0.05	26	<0.05	5
Forgetfulness or poor memory	27	<0.01	16	<0.05	8
Irritability	22	<0.05	13		8
Sleep disturbance	14		19		8

[a]Score of 2 or higher = subjects who reported a score of 2, 3, or 4 for this symptom (scale = 0–4), that is, symptom was at least a mild problem.
[b]p value from Wilcoxon matched-pair test using full range of symptom scores (0–4).
NOTE: RPCS = Rivermead Post-Concussion Symptoms.
SOURCE: Heitger et al., 2007. Reprinted with permission from Journal of Rehabilitation Medicine, 2008. Copyright 2007 by Foundation of Rehabilitation Information.

Stulemeijer and colleagues (2006a) reported on fatigue in 618 consecutive patients 18–60 years old who attended the Radboud University Nijmegen Medical Center in the Netherlands and had mild TBI (impact to the head with GCS 13–15 at admission, with no LOC or LOC less than 30 minutes, and with or without PTA). Controls were 483 people who presented at the emergency department with ankle or wrist distortion. Questionnaires were sent by mail 6 months after trauma and were returned by 299 with mild TBI (52% of the 574 delivered questionnaires) and 287 (60%) of the controls. In both groups, responders were older than nonresponders and more likely to be female. Controls were more highly educated, more likely to be female, and slightly younger, but the analysis adjusted for these characteristics. Fatigue was measured with the Checklist of Individual Strength (CIS), which asks about fatigue severity in the previous 2 weeks. A CIS fatigue score of 40 or higher was used to identify severe fatigue; 95 (32%) of the mild-TBI subjects and 35 (12%) of the controls reported severe fatigue ($p < 0.001$). Limitations of the study include a low response rate.

Gerber and Schraa (1995) conducted a prospective study of 22 consecutively admitted patients who had mild TBI matched with orthopedically injured patients and uninjured controls to assess injury severity, symptoms, and disability. Mild TBI was defined as having sustained an impact to the head with alteration in consciousness including LOC less than 30 minutes or PTA less than 24 hours. Subjects were excluded if they had a GCS of less than 13 or a skull fracture. Orthopedically injured controls included those who had sustained an orthopedic injury of a region other than the head, neck, or upper extremity. Exclusion criteria for both groups included a maximal Abbreviated Injury Score greater than 2, pre-existing history of a learning disability, and chronic medical disorders, major psychiatric disorders, or substance-abuse disorders. An uninjured control group matched for age, sex, and education with the mild-TBI group was

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included. All subjects completed a structured interview with questions about demographic and socioeconomic status and preinjury medical and psychologic status. Subjects were asked about alterations of consciousness, PTA, associated injuries, and symptoms. To evaluate severity of symptoms, the subjects were first asked to describe and rate on a scale medical or psychologic symptoms that they were experiencing at the time (volunteered symptoms). They were also asked to confirm the presence or absence and rate severity of symptoms on a symptom checklist (elicited symptoms). They were contacted for followup at 6 months after injury. At the 6-month followup, 22 (79%) of the 28 mild-TBI subjects and 26 (68%) of the 38 orthopedically injured subjects completed the assessment. In an assessment of symptoms volunteered by the mild-TBI subjects at 6 months after injury, headache was the most frequent volunteered symptom and concentration difficulties (13.6%) and memory problems (13.6%) the most commonly reported cognitive symptoms. Reports of those three symptoms differed significantly among the groups. The mild-TBI group had significantly higher scores for volunteered somatic and cognitive symptom clusters than either control group (each $p < 0.05$). Regarding elicited symptoms at the 6- month followup, fatigue (45.5%) and headache (27.3%) were the symptoms most commonly cited by the mild-TBI group; no symptom was endorsed significantly more by the orthopedic or uninjured controls, and there were no significant differences in the scores for somatic or cognitive symptom clusters. Limitations of the study include the small sample, lack of specification of the method for recruiting community controls, and failure to use appropriate statistical tests to account for small numbers of participants endorsing individual symptoms. Strengths include the consecutive enrollment of injured subjects and careful matching.

Masson (1996) evaluated the prevalence of cognitive, behavioral, and somatic impairments in 231 patients who had sustained mild, moderate, or severe TBI and were hospitalized 5 years before the initiation of the study. The control group consisted of 80 lower-limb–injured (LLI) patients. Subjects were 15–60 years old at the time of injury. One hundred eighty-two TBI patients and 64 LLI patients participated in the followup; 29 (13%) TBI patients and one (1%) LLI patient had died, and 20 (9%) TBI patients and 15 (19%) LLI patients were lost to followup or refused to participate. Self-reported functional status was assessed through face-to-face interviews in the hospital or home, telephone interviews, or postal questionnaires; all LLI cases were assessed with one of these methods. Status was also assessed with the European Chart for Brain Injured Patients Evaluation, and the overall outcome was assessed with the Glasgow Outcome Scale (GOS). Subjective complaints were counted regardless of whether subjects associated them with their injuries. All subjective complaints reported except fatigue and pain were more commonly reported by mild-TBI patients than by LLI patients (see Table 7-4): headache ($p < 0.001$), memory problems ($p < 0.05$), dizziness ($p < 0.01$), anxiety ($p < 0.01$), sleep disturbance ($p < 0.05$), depressive temper ($p < 0.01$), and irritability ($p < 0.01$). Pain was significantly more common in LLI patients ($p < 0.001$). Memory problems, sleep disturbance, pain, and irritability were significantly related to severity in those with TBI, and the severely injured reported them most frequently. Forty-five (39%) mild-TBI patients and six (9%) LLI patients complained of more than three of the eight symptoms (excluding pain) ($p < 0.001$) and could be considered to have PCS according to an ICD-like definition. The rate of PCS in patients with moderate or severe TBI was not reported. Limitations of the study include the lack of face-to-face interviews of LLI patients and the counting of symptoms whether or not they predated injury or were related to a different cause. Strengths include the low loss rate and the population-based nature of the sample.

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TABLE 7.4 Prevalence of Subjective Complaints 5 Years After Injury

	Lower-Limb–Injured Patients (n = 64)			Head Injured Patients According to Initial Head Injury Severity						
				Minor (n = 114)		Moderate (n = 35)		Severe (n = 27)		
Subjective Complaints	No.[b]	%	p[c]	No.[b]	%	No.[b]	%	No.[b]	%	p[a]
Headache	10	15.6	<0.001	50	43.9	19	54.3	12	44.4	NS
Fatigue	19	30.6	NS	34	35.1	11	32.4	15	57.7	NS
Memory problem	10	15.6	<0.05	36	32.1	21	60.0	18	66.7	<0.001
Dizziness	8	12.5	<0.01	37	32.5	13	37.1	7	25.9	NS
Sleep disturbance	8	12.5	<0.05	32	26.3	4	11.4	18	66.7	<0.001
Pain	38	59.4	<0.001	38	33.3	4	11.4	13	48.1	<0.01
Depressive temper	9	14.1	<0.01	44	38.6	17	48.6	11	40.7	NS
Anxiety	9	14.1	<0.01	54	47.4	17	48.6	17	63.0	NS
Irritability	9	14.1	<0.01	43	37.7	21	60.0	17	63.0	<0.05

[a]Prevalences were compared in the three groups of head-injury severity.
[b]Prevalences were calculated among patients who answered the question. Prevalences of overall impairments (related or not related to the head injury by the patient).
[c]Prevalences in lower-limb–injured patients were compared with prevalence in minor–-head-injury patients.
NOTE: NS = not significant.
SOURCE: Masson et al., 1996. Reprinted with permission from Brain Injury. Copyright Taylor and Francis Ltd http://www.informaworld.com.

McLean et al. (1993) assessed psychosocial recovery in 102 hospitalized patients examined at 1 and 12 months after head injury. The subjects were head-injured patients consecutively admitted into Harborview Medical Center in Seattle, WA. Selection criteria included any LOC, PTA for at least 1 hour, and evidence of cerebral trauma; head injury requiring hospitalization; age range of 15–60 years at time of injury; and absence of history of pre-existing conditions, including central nervous system (CNS) insult, major psychiatric problems, and treatment for alcohol-related problems. The reference group consisted of 102 friend controls matched for age, education, sex, and race. Head-injury severity was assessed on the basis of GCS score and time from injury to ability to follow commands consistently. Outcomes were assessed with a battery of psychosocial measures, such as the Head Injury Symptom Checklist (HISC). The HISC includes a list of 12 symptoms that are frequently associated with head injury, for example, headache, dizziness, and concentration problems. At 12 months after injury, the head-injured patients differed significantly in seven symptoms on the HISC: dizziness ($p < 0.01$), blurred vision ($p < 0.001$), concentration problems ($p < 0.001$), being bothered by noise ($p < 0.05$), irritability ($p < 0.01$), temper ($p < 0.01$), and memory problems ($p < 0.001$). The median number of symptoms endorsed at 1 year was five by those with severe TBI, two by those with moderate TBI, three by those with mild TBI, and two by controls. The severely injured reported significantly more symptoms than those with moderate TBI ($p < 0.05$) or friend controls ($p < 0.05$). Limitations of the study include the inability to separate the effects of head injury and other injuries, the absence of a statement of the loss rate before the 1-month assessment, and the relatively small numbers of cases in severity subgroups. Strengths include the recruitment of consecutive cases within days of injury, the use of friend controls who are likely to be similar to those with TBI on difficult-to-measure characteristics, data collection that was primarily face-to-face and consistent in both groups, and the good retention rate between the 1-month and 12-month assessments.

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Secondary Studies

The committee identified three secondary studies. Edna and Cappelen (1987) conducted a prospective study of 485 head-injured patients admitted into surgical and neurosurgical departments in Norway. They found that 51% of the patients reported new PCS after injury (a mean of 4 years after injury). The following new symptoms were reported at a 3- to 5-year followup by over 15% of those with TBI: headaches (23%), memory impairment (20%), dizziness (19%), fatigue (18%), and being bothered by noise or light (18%). The rate of symptoms in controls was reported to be comparable with the rate of preinjury complaints in the head-injured group.

Johansson and colleagues (1991) conducted a population-based study of the incidence of TBI and a retrospective cohort study of symptoms related to head trauma in the Umea district of northern Sweden. Symptoms were collected with a mailed questionnaire 1.5–3 years after injury. Memory impairment was reported by 15% of those with concussion and 63% of those with manifest brain injury ($p < 0.01$, calculated by committee); dizziness by 11% and 45%, respectively ($p < 0.01$); headache by 22% and 45% (not significant); and sensitivity to noise or light by 13% and 36% (not significant). The study was limited by the lack of a control group, although the paper did compare severity groups.

Stulemeijer and colleagues (2006b), in another report based on the primary study described above, compared those who had mild TBI alone or accompanied by other injuries with controls. They found that regardless of whether the mild TBI was isolated, those who had mild TBI had higher scores than controls on each of the physical, affective, and cognitive symptom clusters on the RPQ; each p value comparing the three groups was less than 0.0001, and post hoc comparisons showed that each mild-TBI subset had a higher score than the controls.

There have also been a few studies of military populations and nonmilitary populations (e.g., Walker and Erculei, 1969; Roberts, 1979; Suhr and Gunstad, 2002; Luis et al., 2003; Vanderploeg et al., 2007; and Bryant and Harvey, 1999) that were of interest but did not meet the committee's selection criteria (see Chapter 4). They are not described here, but their findings are consistent with those of the selected studies with regard to postconcussion symptoms.

Summary and Conclusions

The committee reviewed eight primary studies and three secondary studies that assessed the relationship between TBI and self-reported postconcussion symptoms. The study populations consisted largely of patients who presented to an emergency department with mild TBI or who were hospitalized with a broader range of TBI severity.

Six of the eight primary studies were restricted to those with mild TBI. One looked at symptoms reported by soldiers who had recently returned from Iraq and found that significantly more who had had LOC reported each of the nine common postconcussion symptoms; significantly more of those with an altered mental state but no LOC reported five of the nine symptoms (Hoge et al., 2008). Two of the studies evaluated the relationship between TBI and postconcussion symptoms in separate cohorts of people with head trauma involving brief LOC who had been seen in the emergency departments of two hospitals in Kaunas, Lithuania (Mickeviciene et al., 2002; 2004); one of the studies (2002) did not find significant differences between TBI participants and trauma controls in any of the seven postconcussion symptoms

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reported, and the other found significantly higher endorsement of some memory problems, some concentration problems, some dizziness, and extent of fatigue. Stulemeijer et al. (2006a) reported on fatigue in mild-TBI patients who went to an emergency department and in trauma controls and found significantly more fatigue in those with mild TBI at 12 months after injury. Heitger et al. (2007), in a smaller emergency department study, found significantly higher endorsement by mild-TBI patients of eight of 10 symptoms compared with normal volunteers. Gerber and Schraa (1995), a small but well-controlled study, found higher endorsement of headache, memory problems, and concentration problems by mild-TBI patients than by orthopedic-injury patients or community members.

Masson and colleagues (1996) evaluated the prevalence of symptoms in patients in Aquitaine, France, 5 years after hospitalization for head injury. They found that all subjective complaints (headache, memory problems, dizziness, sleep disturbance, and irritability) reported except fatigue were more commonly reported by TBI patients with minor injury than by patients with lower-limb injuries. Memory problems, sleep disturbance, and irritability were significantly related to severity in those with TBI, and the severely injured reported the highest rates. Similarly, McLean et al. (1993) assessed the rate of symptom endorsement by patients 12 months after hospitalization for TBI and by friends who did not experience TBI. They found that at 12 months after injury, the head-injured patients differed significantly in seven symptoms—including dizziness, blurred vision, concentration problems, being bothered by noise, irritability, and memory—but did not differ in headache or fatigue.

Two secondary studies evaluated symptoms in groups that included people with more severe injuries. Johansson et al. (1991) found significantly more dizziness and memory problems in those with more severe injuries than in those with concussion. Headache and sensitivity to noise or light were also endorsed by over one-third of the people with more severe injuries, but the difference was not significant. Edna and Cappelen (1987) found that over 15% of people hospitalized with TBI in surgical or neurosurgical departments endorsed new occurrence of headaches, dizziness, fatigue, memory impairment, and being bothered by noise or light. One secondary study that assessed mild TBI (Stulemeijer et al., 2006b) found that regardless of whether the mild TBI was isolated or accompanied by other injuries, those with mild TBI had higher scores than controls in each of the physical, affective, and cognitive symptom clusters on the RPQ.

The committee concludes, on the basis of its evaluation, that there is sufficient evidence of an association between sustaining a TBI and development of postconcussive symptoms (such as memory problems, dizziness, and irritability).

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TABLE 7.5 Postconcussive Symptoms and TBI

Reference	Study Design	Population	Type of TBI: Mild, Moderate, Severe; Blunt, Penetrating, Blast	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
Mickeviciene et al., 2002	Retrospective cohort	200 head injured patients; 200 non-head injured controls (with minor injury); all patients injured 22–35 mo before study; identified from EDs of two major hospitals in Kaunas, Lithuania	Mild head injury with some LOC but under 15 min.	Self-report questionnaire sent by mail to patients and controls	Headache (during last month) in TBI vs controls: any, 61% vs 61% (p = 0.92); >7 days, 23% vs 23% (p = 0.95); any dizziness, 65% vs 63% (p = 0.84); any memory problems, 68% vs 59% (p = 0.12); any concentration problems, 66% vs 57% (p = 0.08)	Sex- and age-matched controls	Mail questionnaire sent to patients and controls; self-reported symptoms only 131 (66%) head injured patients, 146 (73%) controls returned questionnaires Mild TBI based on clinical assessment without CT scan or MRI No incentive to exaggerate symptoms, because little possibility of receiving monetary compensation for postconcussion symptoms
Mickeviciene et al., 2004	Prospective	300 subjects with concussion matched on age, sex with controls with minor nonhead injuries, followed for 1 year, who presented to EDs of two hospitals in Kaunas, Lithuania	Mild head injury (LOC <15 min)	Questionnaires mailed included standard self-report questionnaire, the RPSQ, VAS for determining symptom severity	At 1 year, headache (during last month), TBI vs controls: any 65% vs 64% (p = 0.98); >7 days, 21% vs 15% (p = 0.15); any dizziness, 62% vs 50% (p = 0.02); any memory problems, 64% vs 47% (p < 0.001); any	Sex- and age-matched controls	Mail questionnaires sent to patients, controls; self-reported symptoms only Mild TBI based on clinical assessment; no traumatic pathologic effects found in 51 cases with CT scans

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Reference	Study Design	Population	Type of TBI: Mild, Moderate, Severe; Blunt, Penetrating, Blast	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
		192 (64%) of head injured patients, 215 (75%) of controls returned questionnaires at 1 year			concentration problems, 71% vs 61% (p = 0.04)		No incentive to exaggerate symptoms, because little possibility of receiving monetary compensation for postconcussion symptoms
Masson et al., 1996	Prospective cohort; population-based study in Aquitane, France, designed to determine incidence of all serious injuries resulting in hospitalization or death	231 head injured with various degrees of head injury; 80 controls with LLI Over 15 to under years old	Mild head injury, 141; moderate head injury, 38; severe head injury, 52; all hospitalized	Self-reported functional status through face-to-face interview in hospital or home, telephone interview, or mailed questionnaire; self-reported functional status assessed with European Chart for Brain Injured Patients Evaluation; overall outcome assessed with GOS	See Table 7-4		Cohort population-based; age and sex distribution similar in all groups Symptom rates include symptoms unrelated to injury After 5 years, following patients not included in final analysis: lower-leg injury, one died, 15 lost to followup; mild head injury, two died, 18 lost to followup; two refused to participate; moderate head injury, two died; severe head injury, 25 died
McLean et al., 1993	Prospective cohort	102 hospitalized adult head injured patients, 102	Broad range of severity	Head Injury Symptom Checklist	At 12 mo after injury, head injured vs friend controls:	Group matched on age, sex, education, race	TBI cases, controls excluded if they had pre-existing

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Reference	Study Design	Population	Type of TBI: Mild, Moderate, Severe; Blunt, Penetrating, Blast	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
		uninjured controls who were friends of head injured patients; 15–60 years old			memory problems, 39% vs 5% ($p < 0.001$); concentration problems, 39% vs 14% ($p < 0.001$); blurred vision, 19% vs 2% ($p < 0.001$); dizziness, 23% vs 6% ($p < 0.01$); irritability, 45% vs 23% ($p < 0.01$); temper, 27% vs 12% ($p < 0.01$); bothered by noise, 27% vs 13% ($p < 0.05$); headache, 36% vs 35%; fatigue, 47% vs 43%; bothered by light, 21% vs 10%; anxiety, 33% vs 26%; insomnia, 27% vs 15%		conditions; head injured cases recruited within days of injury, but loss rate before 1-mo assessment not given; 93% of head injured, 84% of controls seen at 1 mo followed at 1 year; controls were uninjured, so effect may be related to head injury or other injuries.
Gerber and Schraa, 1995	Prospective	22 patients with mild TBI matched with orthopedically injured patients, uninjured controls	Mild	Injury severity, symptoms, disability as measured with structured interview, symptom checklist	% of MTBI patients who volunteered symptoms at followup: headache, 13.6; dizziness, 0; fatigue, 0; concentration problems, 13.6; memory problems, 13.6; irritability, 0 Orthopedic controls	Controls matched on age, sex, education	

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Reference	Study Design	Population	Type of TBI: Mild, Moderate, Severe; Blunt, Penetrating, Blast	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
					volunteered none of listed symptoms; 9.1% of controls volunteered irritability		
Heitger et al., 2007	Prospective cohort	37 patients with mild closed head injury who presented to Christchurch Hospital with acute head injury, 37 controls with no history of head injury	MTBI Patients asked if head injury occurred within 24-h period, it was assessed whether patients remembered being at scene after accident or regaining consciousness, being helped by others, arrival of ambulance, being in ambulance, arriving at hospital, treatment events whose times were noted on chart, being served meal All patients had PTA of 2 min–22 h (median, 15 min); 32 had confirmed LOC (median, 2.0 min; range, 0.5–15 min)	PCS assessed with written versions of RPSQ, RHIFQ, SF-36 Health Survey Patients assessed at 1 week, 3, 6, 12 mo after injury	See Table 7-3	Controls individually matched to each case with respect to age, sex, years of formal education	
Hoge et al., 2008	Retrospective	2,525 US Army infantry soldiers surveyed 3–4 mo	MTBI as assessed with positive responses to any of	Postconcussion symptoms assessed with	See Table 7-2		TBI, symptoms self-reported; assessed with questionnaire

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Reference	Study Design	Population	Type of TBI: Mild, Moderate, Severe; Blunt, Penetrating, Blast	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
		after return from deployment to OIF: 124 head injured with LOC, 260 head injured with altered mental status, 435 with other injury, 1,706 with no injury	following items on questionnaires: "losing. consciousness (knocked out)", "being dazed, confused, or 'seeing stars'", or "not remembering the injury"	Patient Health Questionnaire 15-item somatic symptom severity scale Five questions in addition to questionnaire to assess symptoms related to memory, balance, concentration, ringing in ears, irritability			3–4 mo after deployment; 59%of all soldiers deployed to OIF, on duty completed questionnaire; 7% of values for some variables missing
Stulemeijer et al., 2006a	Prospective cohort	299 consecutively admitted patients 18–60 years old who presented with MTBI at ED of Radboud University Nijmegen Medical Center, assessed 6 mo after trauma Comparison group, 287 patients 18–60 years old who presented to ED with ankle or wrist distortion, assessed 6 mo after trauma	MTBI defined as history of impact to head with or without LOC ≤30 min, with or without PTA and hospital admission with GCS 13–15	Fatigue assessed with Checklist Individual Strength PCS assessed with RPSQ	MTBI patients reported significantly higher levels of fatigue than minor-injury controls (mean score, 29.9 ± 15.3 vs 22.1 ± 12.5; $p < 0.0001$) Severe fatigue in MTBI patients vs controls: 32% vs 12% ($p < 0.001$)		

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NOTE: ED = emergency department, GCS = Glasgow Coma Scale, GOS = Glasgow Outcome Scale, LLI = lower-limb injury, LOC = loss of consciousness, MTBI = mild traumatic brain injury, OIF = Operation Iraqi Freedom, OR = odds ratio, PCS = postconcussion syndrome, PTA = posttraumatic amnesia, RHIFQ = Rivermead Head-Injury Follow-up Questionnaire, RPSQ = Rivermead Postconcussion Symptoms Questionnaire, RR = relative risk, TBI = traumatic brain injury, VAS = Visual Analogue Scale.

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OCULAR AND VISUAL MOTOR DETERIORATION

Ocular and visual motor deterioration is a sensory and neuromuscular anomaly of eye movement that has been characterized by the inability to perform effective saccades, rapid ballistic movements during which there is a suppression of vision (Marr et al, 2005). Some symptoms related to ocular and visual motor deterioration are difficulty in tracking objects visually, lack of coordination, and vertigo.

Primary Studies

The committee identified one primary study that assessed the relationship between TBI and ocular and visual deterioration (see Table 7-6). Heitger and colleagues (2006) assessed oculomotor and upper-limb visuomotor function in 37 patients who had closed-head injuries and presented at the emergency department of Christchurch Hospital in New Zealand. The patients had mild TBI with GCS scores of 13–15. All patients had experienced PTA for about 2 minutes–22 hours; 32 patients had confirmed LOC. The control group consisted of 37 people with no history of TBI or with persisting symptoms or complaints, no central neurologic disorder or psychiatric condition, and no regular intake of psychoactive drugs or history of drug abuse; the controls were individually matched to head-injured patients with respect to age, sex, and years of formal education. The groups were compared at 1 week, 3 months, and 6 months after injury; 31 patients and controls were assessed at 12 months after injury. All participants were evaluated on measures of saccades, oculomotor smooth pursuit, and upper-limb visuomotor function and with neuropsychologic tests. Recovery was assessed with the RPQ. At 3 and 6 months, patients with closed head injuries showed deficits in several oculomotor and upper-limb visuomotor measures and in verbal learning. At 1 year after injury, those with closed head injuries did not show signs of cognitive impairment but had residual deficits in eye and arm motor function.

Secondary Studies

The committee identified one secondary study that assessed the relationship between TBI and ocular and visuomotor function. Kraus et al. (2007) evaluated oculomotor function in people who had sustained TBI. They assessed 37 subjects who had a history of TBI: 20 mild TBI and 17 moderate to severe TBI. Mild TBI was defined as meeting at least one of the following criteria: any period of LOC, any loss of memory of events immediately before or after the incident, any alteration in mental state at the time of the incident, and focal neurologic deficit. Moderate to severe TBI was diagnosed if LOC was greater than 30 minutes or GCS was less than 13. The injuries were sustained at least 6 months before initiation of the study. Subjects were recruited from the University of Illinois Medical Center and through advertisements. Exclusion criteria included history of psychiatric disorder before the head injury, substance abuse, current pending litigation, and presence of another neurologic or medical condition. The control population consisted of 19 healthy people who had no history of psychiatric illness or TBI, substance abuse or dependence, or significant medical or neurologic illness. The groups were matched on age, education, and employment. Subjects underwent a number of oculomotor function and neurocognitive tests: the visually guided saccades (VGS) test, the antisaccades (AS) test, the Tower of London test, the Stroop Color-Word Test, the Paced Auditory Serial Addition Test, the

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Trail Making Test, Conners' Continuous Performance Test-II, the Controlled Oral Word Association Test, the Ruff Figural Fluency Test, and the Wechsler Test of Adult Reading. The patients with moderate to severe TBI showed longer latencies and lower accuracy on the VGS test than the controls, and the patients with mild or moderate to severe TBI had more prosaccade errors on the AS test than the controls.

Summary and Conclusion

The committee reviewed one primary study (Heitger et al., 2006) and one secondary study (Kraus et al., 2007) that assessed the relationship between TBI and ocular and visual motor deterioration. The results showed a slight deterioration in ocular and visual motor function after a mild (closed) TBI. Heitger and colleagues (2006) found that at 6 months after injury, patients with closed head injuries showed deficits on several ocular and upper-limb visual motor measures. At 1 year after injury, those with closed head injuries did not show signs of cognitive impairment but had residual deficits in eye and arm motor function. Kraus and colleagues (2007) found that the patients with moderate to severe TBI had longer latencies and lower accuracy than controls on the VGS test; patients with mild or moderate to severe TBI had more prosaccade errors than controls on the AS test.

Although the primary study found a decline in ocular and visual motor function after mild (closed) head injury, the overall body of evidence on this outcome is limited in that only two studies met the committee's criteria for inclusion as either primary or secondary.

The committee concludes, on the basis of its evaluation, that there is limited/suggestive evidence of an association between sustaining a mild TBI and the development of ocular and visual motor deterioration.

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TABLE 7.6 Ocular and Visual Motor Deterioration and TBI

Reference	Study Design	Population	Type of TBI	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
Heitger et al., 2006	Prospective cohort	37 mild closed–head-injury patients from ED at Christchurch Hospital, New Zealand	Mild closed head injury (GCS, 13-15)	Saccades, oculomotor smooth pursuit, upper-limb visuomotor function, neuropsychologic tests; recovery assessed with RPSQ	Sustained motor impairment up to 1 year	Controls matched with respect to age, sex, years of formal education	

NOTE: ED = emergency department, GCS = Glasgow Coma Scale, RPSQ = Rivermead Postconcussion Symptoms Questionnaire, TBI = traumatic brain injury

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ENDOCRINE DISORDERS

The endocrine system consists of glands that secrete hormones that regulate a host of functions, including metabolism, growth, and development. The pituitary gland, in the base of the brain, can be damaged during TBI. The pituitary secretes hormones that regulate homeostasis and hormones that stimulate other endocrine glands. The hypothalamus, in the middle of the base of the brain, is responsible for regulating body temperature, hunger, thirst, and fatigue and for synthesizing and secreting hypothalamic releasing factors that stimulate pituitary hormone release.

Clinical data suggest that TBI can cause complex hormonal responses of hypothalamo–pituitary–end organ axes that lead to acute and chronic hypopituitarism (Cernak et al., 1999; Woolf, 1992; Klose et al., 2007b). The most frequent dysfunctions are growth hormone (GH) deficiency (Bavisetty et al., 2008), secondary hypoadrenalism, hypogonadism (Cernak et al., 1997; Woolf, 1986; Kosteljanetz et al., 1981), hypothyroidism (Woolf et al., 1988; Shutov et al., 1980; Shutov and Chudinov, 1987, 1988, 1993), and diabetes insipidus (Klose et al., 2007a; Giordano et al., 2005; Behan et al., 2008; Boughey et al., 2004; Tsagarakis et al., 2005). It has been reported that the risk of pituitary insufficiency increases in patients who have severe TBI but not mild TBI. It has been hypothesized that neuroendocrine changes after TBI might be consequences of both structural and functional hypothalamo-pituitary changes (Klose et al., 2007b; Woolf 1986). That hormonal alterations substantially modify the posttraumatic clinical course and the success of therapy and rehabilitation underscores the need for the identification and appropriate timely management of hormone deficiencies to optimize patient recovery from head trauma, to improve quality of life, and to avoid the long-term adverse consequences of untreated hypopituitarism.

The committee reviewed several studies of damage to the pituitary gland and hypothalamus and possible adverse effects (including diabetes insipidus, hypopituitarism, and GH insufficiency); they are discussed below.

Primary Studies

The committee identified eight primary studies that assessed the relationship between TBI and a variety of endocrine disorders, including diabetes insipidus (DI), GH insufficiency, and hypopituitarism (see Table 7-7 for a summary of the primary studies).

Agha et al. (2005b) prospectively studied the effect of TBI on posterior pituitary function, specifically DI and the syndrome of inappropriate antidiuretic hormone secretion (SIADH), in 50 consecutive patients (38 men and 12 women). The patients were admitted into a neurosurgical unit of a hospital in Dublin, Ireland, and had a median age of 35 years and an initial GCS score of 3–13; they were compared with 27 healthy controls matched for age, sex, and body-mass index (BMI). All subjects were assessed three times: during the acute phase, at 6 months after trauma, and at 12 months after trauma. Posterior pituitary function in the acute phase was assessed by determining serial daily fluid balance (serum and urine osmolalities) and serum sodium and with the standard observed 8-hour water-deprivation test; at 6 and 12 months, only the water-deprivation test was used. In the acute phase, DI was seen in 13 (26%) patients, 11 of whom received the diagnosis on the basis of hypernatremia associated with hypotonic

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polyuria and two on the basis of the water-deprivation test. The development of DI was associated with a lower GCS score, but the association was not significant; in the acute phase, however, there was a negative association between peak plasma osmolality and GCS scores (r, -0.39; p = 0.005) and GOS scores (r, -0.45; p = 0.001). At 6 months, nine of the patients had normal water-deprivation tests, leaving four of 48 patients with TBI and none of 27 controls with DI; at 12 months, an additional patient had recovered; no new cases were observed at either followup time. Two of the three patients with permanent DI had partial vasopressin deficiency. In the acute phase, seven (14%) patients had SIADH, and there was no association of SIADH with any patient variable. The SIADH had resolved in all patients by 6 months, and no new cases were reported.

Agha et al. (2005a) used a longitudinal design to assess pituitary function in 50 consecutive patients who had severe or moderate TBI. GH deficiency was found in nine (18%) patients in the acute phase; five recovered after 6 months, and two more developed deficiency. At the 1-year followup, five (10%) had GH deficiency.

In 2004, Agha et al. (2004a) prospectively studied the effect of moderate or severe TBI on anterior pituitary dysfunction in 102 consecutive patients admitted into a neurosurgical unit in Beaumont Hospital in 2000–2002. The TBI cohort did not overlap with that in the study above (Agha et al., 2005a). The control population consisted of 31 healthy people matched to cases on age, sex, and BMI. Forty-two patients had sustained moderate TBI, defined as having a GCS score of 9–13; 57 had sustained severe TBI, defined as a GCS score of 8 or less. Exclusion criteria included being over 65 years old or under 15 years old at the time of testing, having suffered a prolonged hypotensive episode, being pregnant, and being on glycocorticoid therapy. Patients were tested at 6–36 months after injury (median, 17 months). The glucagon stimulation test (GST) was used to screen for somatotrophic and corticotrophic function. Those with abnormal GH response related to GST were given the insulin tolerance test (ITT), and those with a history of heart disease or seizures were given the arginine + growth-hormone–releasing hormone (GHRH) test. Those with subnormal serum cortisol responses to the GST were given the ITT or, if they had heart disease or seizures, were given the 250-µg short synacthen test (SST). The authors found that 18 (17.6%) of the injured patients and no controls had a GH response to the GST test of less than 5 µg/L; 11 of the 18 failed the ITT or the arginine + GHRH test. In addition, 23 (22.5%) of the TBI patients, and three (9%) of the 31 controls had cortisol responses to GST of less than 450 nmol/L; 13 of these TBI patients failed the ITT or synacthen test.

Agha et al. (2004b), using the same cohort (Agha et al., 2004a), prospectively studied the incidence of posterior pituitary dysfunction (including DI) in 102 consecutive patients who had sustained moderate or severe TBI and 27 healthy matched controls. Patients were evaluated 6–36 months after injury. In the acute phase, 22 (21.6%) patients developed DI. Seven (6.9%) of the patients had permanent DI compared with none of the controls. In the acute phase, 13 (12.7%) patients (95% confidence interval [CI], 7.0–20.8%) had evidence of SIADH. At followup, two patients had evidence of SIADH.

Kelly and colleagues (2006) conducted a prospective cohort study of GH deficiency or insufficiency after TBI. Of 129 patients who were admitted into an intensive-care unit and who had sustained mild TBI (GCS score, 13–14), moderate TBI (GCS score, 9–12), or severe TBI (GCS score, 3–8), 44 were compared with 41 healthy controls. The subjects participated in a variety of pituitary-function tests and neurobehavioral and quality-of-life tests at 6–9 months

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after injury. At 6–9 months after injury, eight (18%) TBI patients had GH deficiency or insufficiency; the cutoff was defined by the lower 10% of controls (p = 0.35). Limitations of the study include a low followup rate and a small sample that yielded low power to detect a difference in rates.

Herrmann and colleagues (2006) assessed the prevalence of hypopituitarism in 76 patients who had sustained severe TBI. The patients were evaluated in July 2003–May 2004 and had been discharged from neurosurgery departments of a number of hospitals in Germany. Severe TBI was defined as having a GCS score of less than 8 (mean, 4.4 ± 2.8); patients were injured an average of 22 ± 10 months before the study. TBI was characterized with CT and MRI. Exclusion criteria included alcohol abuse, known pituitary deficiency or disease, apallic syndrome (vegetative state) or illness that would prevent testing, and pregnancy. Patients underwent a series of neuroendocrine tests, including GH response to GHRH + arginine, thyroid-stimulating hormone (TSH), free thyroxine, thyroxine (T_4), triiodothyronine (T_3), prolactin, testosterone, estradiol, sex-hormone–binding globulin, cortisol, adrenocorticotropic hormone (ACTH), GH, and insulin-like growth factor 1 (IGF-1). Of the patients, 18 (24%) were found to have pituitary deficiency, six (8%) had GH insufficiency, two patients (3%) had partial ACTH deficiency, and two had TSH deficiency.

Schneider and colleagues (2006) conducted a prospective longitudinal study of TBI patients to assess hypopituitarism at 3 and 12 months after injury. The study population consisted of 78 consecutively admitted TBI patients. The control group consisted of 38 healthy subjects. Inclusion criteria were TBI grades I–III[3] as assessed according to GCS, BMI of 17–20, and age of 18–65 years. Exclusion criteria were glucocortoid treatment within 3 weeks or GH treatment within 12 months; a history of cranial irradiation or pre-existing pituitary disease; severe cardiac, renal, or hepatic disease; sepsis; and substance abuse. Subjects were evaluated with the GHRH + arginine test, the short ACTH test, and basal hormone measurements. Seventy of the patients participated in the followup at 12 months after injury. The authors found that more than 50% of the patients had impairments of at least one pituitary axis at 3 months after injury. At 12 months, 36% still had hormonal disturbances. Seven (10%) had stimulated GH less than 9 ng/mL, as did one of the 38 controls (not significant). The following axes were affected at 12 months after injury: 21% gonadotropic, 10% somatotropic, 9% corticotropic, and 3% thyrotropic.

Klose et al. (2007b) conducted a 12-month prospective cohort study to assess the incidence of hypopituitarism after TBI. They assessed 46 patients hospitalized at the Copenhagen University Hospital with mild (22), moderate (nine), or severe (15) TBI for hypopituitary function at 3, 6, and 12 months after injury. Mild TBI was defined as a GCS of 13–15, moderate 9–12, and severe under 9. The control group consisted of 30 age- and BMI-matched healthy volunteers who underwent anterior pituitary testing. Another cohort of 100 healthy volunteers served as controls for the Synacthen test. Anterior pituitary function was assessed initially at 0–12 days after injury for baseline information and then retested at 3, 6, and 12 months after injury. Tests included the ITT for baseline and poststimulatory hormone levels or, if this test was contraindicated, the GHRH + arginine test. A synacthen test to assess baseline hormone concentrations was conducted at 6 months. At 3 months after injury, six of the 46 patients had anterior pituitary deficiencies; at 12 months after injury, no additional patients had

[3] A GCS of 3-8 indicates a severe TBI or a grade III, while a GCS of 9-12 indicates a moderate TBI (grade II), and a GCS of 13-15 indicates a mild TBI or grade I.

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deficiencies. Of the 46 patients, five (11%) had GH deficiencies. Patients with more severe TBI were more likely to be hypopituitary (four) than those with mild or moderate TBI (one) ($p = 0.02$). TBI severity appeared to be related to early endocrine changes, such as increased total cortisol, free cortisol, and copeptin and decreased thyroid and gonadal hormones ($p < 0.05$). Severity of TBI was not related to long-term development of hypopituitarism ($p > 0.1$).

Secondary Studies

The committee identified 4 secondary studies that assessed the relationship between TBI and a variety of endocrine disorders, including DI, GH insufficiency, and hypopituitarism.

In a study of pituitary function in competitive boxers, Kelestimur et al. (2004) studied 11 male Turkish active or retired amateur boxers and compared them with seven nonboxing controls matched on age and BMI. Radioimmunoassays were used to assess free T4, free T3, TSH, follicle-stimulating hormone (FSH), prolactin, cortisol, luteinizing hormone, total testosterone, free testosterone, and IGF-1. Serum GH secretory status was assessed with the GHRH plus GH-releasing peptide-6 (GHRH + GHRP-6) test. Basal hormone levels in all boxers and controls were within normal limits. However, there was a statistically significant difference in mean peak GH levels, which were 10.9 ± 1.7 μg/L in the boxers and 41.4 ± 6.7 μg/L in the controls; five (45%) of the boxers were considered to have severe GH deficiency (less than 10μg/L). Mean IFG-1 levels were significantly higher in the controls (367 ± 18.8 ng/mL) than in the boxers (237 ± 23.3 ng/dL). Other pituitary hormones were normal, including antidiuretic hormone. There was a significant negative correlation between peak GH and duration of boxing (r, -0.60) and bouts of boxing (r, -0.61).

In a similar study, Tanriverdi et al. (2007) compared pituitary function in 22 active or retired amateur competitive Turkish kick boxers (16 men and six women) with that in 22 nonboxing controls (17 men and five women) that were matched on age and sex. The following basal hormone levels were measured: free T4, free T3, TSH, FSH, prolactin, luteinizing hormone, total testosterone, estradiol, gonadrotropin, cortisol, and IGF-1. The GHRH + GHRP-6 test was used to assess GH. As with the Turkish boxers in the previous study, the basal hormone levels in the kick boxers did not differ from those in the controls except for IGF-1 levels, which were significantly lower in the kick boxers (276.5 ± 25.9 ng/mL) than in the controls (346.8 ± 20.9 ng/mL). Five of the kick boxers had peak GH of less than 20μg/L and were considered to be GH-deficient; they also were older and had boxed longer and in more bouts than boxers who were not deficient, but the difference was not significant. Two boxers were also deficient for cortisol, one of whom was also GH-deficient. As with the regular boxers in the previous study, there was a significant negative correlation between IGF-1 and age, duration of boxing, and number of bouts.

Bushnik and colleagues (2007) conducted an observational study of 64 people to assess neuroendocrine outcomes and fatigue after TBI. Subjects were recruited from the community with flyers. Over one-third of the study population had self-reported coma of more than 2 weeks. The subjects underwent neuroendocrine testing an average of 10 years after injury, including tests to assess thyroid, adrenal, gonadal axes function and GH after glucagon stimulation. The authors found that 23 subjects (39%) had severe GH deficiency, 16 (27%) had moderate GH deficiency, and 20 (34%) had normal GH reserve following glucagon administration. Twelve (19%) of the 63 participants had central hypothyroidism. Forty percent (23/57) of the subjects

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were deficient in one anterior pituitary axis, 44% (25/57) were deficient in two, and 9% (5/57) were deficient in more than two.

As discussed in Chapter 5, Roberts (1979) assessed patients for disordered hypothalamic and pituitary function. Results indicated that anterior hypopituitarism did not increase in frequency because of head trauma; at the time of the study, only one patient (a 10-year-old boy) had that diagnosis. The incidence of DI (diagnosed on the basis of polyuria) in the consecutive series was eight of 291 patients (3%). Hypothalamic hyperphagia was diagnosed in 16 of 291 (6%) in the consecutive series and six of 40 (15%) in the selected series. Lower age and greater severity of injury seem to contribute to increased rates of DI and hyperphasia in the injured.

Summary and Conclusions

Changes in the endocrine system after TBI have been reported. The committee identified eight primary and four secondary studies that assessed the relationship between TBI and a number of endocrine disorders, including hypopituitarism, DI, and GH insufficiency.

Hypopituitarism

Regarding hypopituitarism, the committee identified one primary study (Agha et al., 2005b) and four secondary studies (Bushnik et al., 2007; Roberts, 1979; Kelestimur et al., 2004; Tanriverdi et al., 2007) that assessed the relationship between TBI and hypopituitarism. Many of the reported disturbances appear acutely and eventually resolve, but several studies reviewed by the committee demonstrate some long-term effects of hypopituitarism (Agha et al., 2005b; Kelestimur et al., 2004; Tanriverdi et al., 2007).

The committee concludes, on the basis of its evaluation, that there is sufficient evidence of an association between moderate or severe TBI and endocrine dysfunction, particularly hypopituitarism.

Diabetes Insipidus

The committee identified two primary studies (Agha et al., 2005b, 2004b) that evaluated the relationship between TBI and DI. Agha et al. (2005b) prospectively studied the effects of TBI on posterior pituitary function, including DI, and found that the development of DI was associated with lower GCS score, but the association was not statistically significant. In the acute phase, there was a negative association between peak plasma osmolality and GCS and GOS scores. At followup, four (8%) TBI subjects and no controls had DI. Agha et al. (2004b) prospectively studied the incidence of posterior pituitary dysfunction (including DI) in consecutive patients who had sustained moderate or severe TBI and healthy matched controls. Seven percent of patients who had moderate or severe TBI and no controls had permanent DI.

The committee concludes, on the basis of its evaluation, that there is limited/suggestive evidence of an association between moderate or severe TBI and diabetes insipidus.

Growth Hormone Insufficiency

The committee identified five primary studies (Agha et al., 2004a,b, 2005a,b; Kelly et al., 2006) that assessed the relationship between TBI and GH insufficiency.

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In 2004, Agha et al. (2004a) prospectively studied the effect of moderate or severe TBI on anterior pituitary dysfunction in 102 consecutive patients and found that 18 had a GH response to the GST test of less than 5 µg/L; 11 of these patients failed the ITT or the arginine + GHRH test. In addition, 23 TBI patients had cortisol responses to GST of less than 450 nmol/L; 13 of these failed the ITT or synacthen test. Similarly, Agha et al. (2005a) assessed pituitary function in the same population of 50 consecutive patients with severe or moderate TBI. GH deficiency was found in nine (18%) subjects in the acute phase; five recovered after 6 months, and two more patients developed deficiency. At the 1-year followup, five were GH-deficient.

Kelly et al. (2006) conducted a prospective cohort study of GH deficiency or insufficiency after TBI and found that at 6–9 months after injury, eight (18%) TBI patients had GH deficiency or insufficiency when the cutoff was defined by the value in the lower 10% of controls.

The committee concludes, on the basis of its evaluation, that there is sufficient evidence of an association between moderate or severe TBI and growth hormone insufficiency.

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TABLE 7.7 Endocrine Disorders and TBI

Reference	Study Design	Population	Type of TBI	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
Agha et al., 2004a	Cohort	102 patients, including 85 males; median age, 28 years; range, 15–65 years; TBI survivors admitted into neurosurgical unit in Beaumont Hospital in 2000–2002; examined at median of 17 mo (range, 6–36 mo) after event; 31 matched healthy controls	Severe or moderate (GCS score, 3–13)	GH, ACTH assessed with GST; ITT or arginine + GHRH test for GH assessment; ITT or 250-µg short Synacthen test for ACTH reserve	Controls: normal response to GST was stimulated peak of >5 µg /L, cortisol peak > 450 nmol/Liter (16 µg/dL) 18 TBI patients (17.6%), 0 controls had GH response to GST test of <5 µg/L, 11 of whom failed ITT or arginine + GHRH test 23 patients (22.5%), three of 31 (9%) of controls had cortisol responses to GST of <450 nmol/L, 13 of whom also failed ITT or Synacthen test	Matched on age, sex, BMI	Inclusion criteria: severe or moderate TBI, age 15–65 years, 6 mo or longer after injury, discharged alive from neurosurgical unit 29% had history of seizure disorder GH or ACTH deficiency not related to age, GCS score, or presence of other pituitary hormone abnormalities
Agha et al., 2004b	Prospective cohort	Same population as Agha et al., 2004a	Moderate, defined as GCS score of 9–13 Severe TBI defined as GCS score of 8 or less	WDT; plasma, urine osmolalities; urine volume; thirst score; blood pressure; weight; plasma sodium	In acute phase, 22 (21.6%) patients developed DI Seven of 102 patients who sustained moderate or severe TBI had permanent DI (6.9%) vs 0 of 27 controls In acute phase, 13 subjects (12.7%; 95% CI, 7.0%–20.8%) had evidence of SIADH; at followup, two patients had evidence of SIADH	Matched on age, sex, BMI	Inclusion criteria: severe or moderate TBI, age 15–65 years, at least 6 mo after injury Exclusion criteria: pregnant women, patients with established renal disease, patients with raised creatinine, patients on lithium of other medication known to cause renal insensitivity to AVP, patients with

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Reference	Study Design	Population	Type of TBI	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
							diabetes mellitus and hemoglobin A1C greater than 6.5%, patients with hypokalemia or hypercalcemia
Agha et al., 2005b	Prospective cohort	50 patients with severe or moderate TBI; studied acutely, at 6, 12 mo after TBI; 27 healthy controls	Severe or moderate; GCS score 3–13	Pituitary function; posttraumatic DI; SIADH	13 patients (26%) had DI in acute phase, of whom nine recovered by 6 mo, additional patient recovered by 12 mo; 0 of 27 controls had DI Three patients had permanent DI, including two with partial vasopressin deficiency Seven patients had SIADH in acute phase, but none at 6 or 12 mo	Matched on age, sex, BMI	Posterior pituitary dysfunction seen in acute phase after TBI but most patients recover over long term
Agha et al., 2005a	Prospective cohort	50 patients with severe or moderate TBI; studied acutely, at 6, 12 mo after TBI; 27 healthy controls	Severe or moderate; GCS score 3–13.	Pituitary function	GH deficiency found in nine subjects (18%) in acute phase; five recovered after 6 mo; two more patients developed deficiency; at 1-year followup, five had GH deficiency	Matched on age, sex, BMI	
Herrmann et al., 2006	Cohort	76 patients with severe TBI, discharged from neurosurgery departments in Germany	Severe, defined as GCS score <8; mean, 4.4 ± 2.8; patients injured average of 22 ± 10 mo before study	Neuroendocrine tests, including GH response to GHRH + arginine; TSH; free T4, T4, T3; prolactin; testosterone;	18 of 76 had pituitary deficiency Six of 76 had GHD (GH peak range [GHRH + arginine], 2.8–6.3 µg/L; GH peak range [ITT], 1.5–2.2		No control group, no indication of percentage of normals outside reference range

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Reference	Study Design	Population	Type of TBI	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
				estradiol; SHBG; cortisol; ACTH; GH; IGF-I	µg/L; IGF-I range, 62–174 µg/L) Two of 76 had partial ACTH deficiency Two of 76 had TSH deficiency		
Kelly et al., 2006	Prospective	44 patients, 14–80 years old, with mild, moderate, or severe TBI with GHD or GH insufficiency; 41 healthy controls	Mild, moderate, severe (GCS score 3–14)	Pituitary function; neurobehavioral, QOL testing performed 6–9 mo after injury	Eight of 44 (18%) had GHD/GHI vs 10% of controls; 6–9 mo after injury, TBI patients with GHD/GHI had higher rates of at least one marker of depression ($p < 0.01$) TBI patients with GHD/GHI had decline in QOL (by SF-36 Health Survey) due to physical health ($p = 0.02$); energy and fatigue ($p = 0.05$); emotional well-being ($p = 0.02$); pain ($p = 0.01$); general health ($p = 0.05$)		After complicated mild, moderate, or severe TBI, 18% of patients develop chronic GHD/GHI, which is associated with depression, poor QOL
Klose et al., 2007b	Prospective	46 consecutive patients with mild (22), moderate (nine), or severe (15) TBI hospitalized in Copenhagen University Hospital; 30 healthy volunteer controls; another 100 healthy volunteer controls for	Mild, GCS 13–15; moderate, GCS 9–12; severe, GCS <9	Pituitary insufficiency assessed at 3, 6, 12 mo Baseline, stimulated hormone concentrations; Synacthen-test (acute + 6 mo);	3 mo after trauma, six of 46 had anterior pituitary deficiencies 12 mo after trauma, one patient recovered; no additional patients found to have deficiencies Five of 46 had GH deficiency at 12 mo Four of 15 patients	Age, BMI	Exclusion criteria: inconclusive diagnosis, chronic alcohol or drug abuse, prior severe head trauma or apoplexies, chronic use of glucocorticoids Mean GH not significantly

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Reference	Study Design	Population	Type of TBI	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
		Synacthen test		ITT, GHRH + arginine test (used if ITT was contraindicated at 3, 12 mo)	with severe TBI had hypotituitarism vs one of 31 patients with mild or moderate TBI		different from controls at 3, 12 mo; number of controls with hormone deficiency not given
Schneider et al., 2006	Prospective longitudinal	78 consecutively admitted patients with TBI of whom 70 were tested at 12 mo; 38 healthy controls	Grade I–III as assessed with GCS	Subjects evaluated at 3, 12 mo after inury with GHRH + arginine test, short ACTH test, basal hormone measurements	3 mo after trauma, 56% had impairments of at least one pituitary axis with axes being affected as follows: gonadotropic, 32%; corticotropic, 19%; somatotropic, 9%; thyrotropic, 8% 12 mo after trauma, 36% still had impairments; affected following axes: gonadotropic, 21%; somatotropic, 10%; corticotropic, 9%; thyrotropic, 3%; seven of 70 had stimulated GH < 9 ng/mL vs one of 38 controls (not significant)		Exclusion criteria included glucocorticoid treatment within 3 weeks or growth hormone treatment within 12 mo; history of cranial irradiation, pre-existing pituitary diseases; severe cardiac, renal, or hepatic disease; sepsis; substance abuse Except for stimulated GH, no indication of percentage of normals outside reference range

NOTE: ACTH = adrenocorticotropic hormone, AVP = arginine vasopressin, BMI = body-mass index, CI = confidence interval, DI = diabetes insipidus, FSH = follicle-stimulating hormone, GCS = Glasgow Coma Scale, GH = growth hormone, GHD = growth-hormone deficiency, GHI = growth hormone insufficiency, GHRH = growth-hormone releasing hormone, GST = Glucagon Stimulation Test, IGF-1 = insulin-like growth factor-1, ITT = insulin-tolerance test, QOL = quality of life, TBI = traumatic brain injury, SHBG = sex-hormone binding globulin, SIADH = syndrome of inappropriate antidiuretic hormone secretion, TSH = thyroid-stimulating hormone, WDT = water-deprivation test.

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NEURODEGENERATIVE DISEASES

Neurodegenerative diseases refer to a variety of nervous system disorders that result from the deterioration of neurons or their myelin sheath. Such deterioration can lead to a number of debilitating diseases. The committee members focused specifically on dementia of the Alzheimer type, parkinsonism, and multiple sclerosis (MS) because those were the neurodegenerative diseases that were identified during the TBI literature searches. Neurodegenerative disorders are commonly categorized into ones that primarily affect memory and lead to dementia, such as Alzheimer's disease (AD), and ones that affect movement, such as ataxia, including Parkinson disease (PD) and MS.

DEMENTIA OF THE ALZHEIMER'S TYPE

AD is a progressive neurodegenerative illness that is characterized by the presence of amyloid plaques and neurofibrillary tangles in the brain. Advanced age is an important risk factor for AD inasmuch as it is most commonly observed in people 65 years old and older. It has been estimated that about 4.5 million people in the United States suffer from AD and that about 5% of men and women 65–74 years old have it; nearly 50% of those 85 years old and older may have AD (NIH 2006). Symptoms of AD vary widely with the stage of the illness. In the early stages, symptoms commonly include memory impairment, which can progress to severe cognitive decrements and an inability to perform daily functions. Symptoms also include difficulty with language and poor judgment. The duration of the disease is estimated to be 5–20 years. Genetics may play a role in the development of AD: researchers have found that the presence of the APOE gene is a risk factor for such diseases as cardiovascular disease, atherosclerosis, and dementia (including AD). Because pathologic confirmation of the clinical diagnosis of AD was not reported in most of the studies reviewed, the committee limited its conclusions to the evaluation of the relationship of TBI and dementia of the Alzheimer's type, rather than AD.

The committee identified one primary study that investigated the association between TBI and dementia of the Alzheimer's type. Plassman et al. (2000) investigated the relationship between nonpenetrating head injury and the risk of AD and other dementias in WWII veterans (see Table 7-8).

Primary Study

Plassman et al. (2000) conducted a population-based retrospective cohort study of male WWII Navy and Marine Corps veterans to assess the relationship between nonpenetrating TBI and the risk of AD and other dementias. Subjects included 548 veterans who served during 1944–1945 and were hospitalized during military service with diagnosis of nonpenetrating head injury; 1,228 subjects matched on education and age who had unrelated injuries served as controls. Medical records were abstracted in 1996 and 1997 to document details of the closed head injuries. Subjects were considered to have had a closed head injury if it was documented in medical records; if the injury produced LOC, PTA, or skull fracture; and if the injury did not result in marked cognitive impairment or neurologic sequelae more than 3 months after injury. Subjects who had a head injury that penetrated the dura mater were excluded from the study. TBI

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was designated as mild (LOC or PTA for less than 30 minutes with no skull fracture), moderate (LOC or PTA for more than 30 minutes but less than 24 hours and/or skull fracture), or severe (LOC or PTA for more than 24 hours). The authors identified men with dementia by using a three-stage screening and assessment process, including a telephone interview, a dementia questionnaire, and a clinical assessment for those whose scores indicated dementia. Proportional-hazards methods were used to estimate the risk of AD and dementia associated with head injury. Multiple logistic regression was also used to assess the validity of the proportional-hazards analysis. The authors found that a history of moderate TBI increased the risk of AD (hazard ratio [HR], 2.32; 95% CI, 1.04–5.17), as did severe TBI (HR, 4.51; 95% CI, 1.77–11.47). Similarly, moderate TBI (HR, 2.39; 95% CI, 1.24–4.58) and severe TBI (HR, 4.48; 95% CI, 2.09–9.63) were associated with dementia. There was no significant risk of AD (HR, 0.76; 95% CI, 0.18–3.29) or dementia (HR, 1.33; 95% CI, 0.51–3.47) in those with mild TBI. The study is limited in that the data rely primarily on reviews of 50-year-old medical records and the authors could not rule out other factors in the development of dementia later in life.

Secondary Studies

The committee identified nine secondary studies that assessed the relationship between TBI and AD. Schofield and colleagues (1997) conducted a community-based longitudinal study of aging that included 271 participants in north Manhattan. The participants were screened for significant cognitive impairment. History of TBI was ascertained on two occasions, first by physicians who asked about head injury with LOC and second by an interviewer who asked about prior TBI with LOC or PTA, duration of LOC, and date of head injury. Annual evaluations for up to 5 years were conducted to determine the first occurrence of dementia. The annual examination consisted of a clinical evaluation by a physician and neuropsychologic testing, including tests of memory, abstract reasoning, language, and tests of construction. Of the 217 participants, 39 had a diagnosis of probable or possible AD. A history of TBI with LOC as reported to a physician was associated with earlier onset of dementia due to AD (relative risk [RR], 4.1; 95% CI, 1.3–12.7). However, a history of TBI with LOC or PTA as reported to an interviewer was not significantly associated with earlier onset of AD overall (RR, 2.0; 95% CI, 0.7–6.2), but those who reported LOC of over 5 minutes were at increased risk (RR, 11.2; 95% CI, 2.3–59.8). The authors also found that incident AD was significantly associated with TBI that had occurred within the preceding 30 years (RR, 5.4; 95% CI, 1.5–19.5).

French and colleagues (1985) conducted a case-control study to assess risk factors related to dementia of the Alzheimer type. The study population included 78 male subjects who received a diagnosis of AD in 1979–1982 at the Veterans' Administration Medical Center in Minneapolis, MN, and controls matched to subjects on age, race, and sex. Inclusion criteria included "insidious onset, gradual progression of dementia with an intact level of consciousness, and absence of focal neurologic signs". Interviews were held with surrogate respondents (usually next of kin). Information ascertained during the interview included variables relevant to viral, genetic, and immunologic hypotheses; environmental and occupational exposures; drug use; psychologic stress; smoking; and alcohol use. Information about prior TBI was also ascertained. The authors found that TBI was reported significantly more frequently in subjects than in hospital controls (OR, 4.50; 95% CI, 1.44–15.69; $p < 0.01$), and TBI occurred before the diagnosis of dementia.

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Amaducci and colleagues (1986) conducted a case–control study in a population of 152 consecutive patients admitted into neurology departments of seven centers in northern Italy in 1982–1983 who had a clinical diagnosis of AD. Clinical history, a neurologic examination, and neuropsychologic and laboratory tests were used to assess other factors, including TBI. The control group consisted of 116 hospital and 92 population controls matched to the subjects on age, sex, and region of residence. The authors found that although the odds of TBI were higher in subjects than in hospital controls (OR, 3.5; $p = 0.18$) or population controls (OR, 2.0; $p = 0.51$), the differences were not significant.

Broe and colleagues (1990) conducted a case–control study of 170 people who had a clinical diagnosis of AD and 170 controls matched to the cases on age, sex, and region of residence. Subjects were consecutive new referrals to dementia clinics in Sydney, Australia, who were 52–96 years old. The participants and accompanying relatives or friends were interviewed to assess cognitive or behavioral changes. A clinical examination included a Neurology of Aging Schedule, the Mini-Mental State Examination (MMSE), and a full neuropsychologic assessment. The authors defined a significant TBI as one resulting in LOC for more than 15 minutes. The estimated ORs for head injuries were relatively low, and none was statistically significant. The OR for TBI in all subjects any time before the assessment was 1.33 ($p = 0.593$) and for head injuries in all subjects at least 10 years before the assessment 1.60 ($p = 0.405$).

Heyman and colleagues (1984) conducted a case–control study to assess risk factors for AD. Participants were 40 patients with onset of dementia and 80 controls matched on age, sex, and race. A structured interview was administered to acquire information about a variety of risk factors, including prior illnesses, dietary or lifestyle habits, occupational exposure, exposure to domesticated and wild animals, and family history of dementia, mental retardation, and leukemia. Both subjects and close family members or friends were interviewed. Each of the 40 patients with a diagnosis of AD was also admitted for a uniform battery of diagnostic testing. Six of the subjects had sustained TBI, and four of them reported that the incident occurred 30–40 years before the onset of dementia; in one case, the injury had occurred 19 years earlier. In all five patients, the reported TBI was severe and was associated with LOC, PTA, and multiple fractures of the limbs or trunk. The authors found that a history of TBI was reported significantly more frequently in the subjects than in the controls (15.0% and 3.8%, respectively).

As discussed above, Lewin et al. (1979) determined the cause of death of 75 severely injured patients discharged from the John Radcliffe Infirmary in Oxford, England, 10–24 years earlier who had been in a consecutive series of 7,000 patients with severe TBI (patients had LOC for 1 week or more). The authors found that "most patients who survived in states of decerebrate dementia died within a year after injury, and though a few lived for several years, only one from the two series survived for a decade." In addition, frontolimbic dementia, seen in 50 cases, was observed only after the most severe form of TBI and was largely confined to adolescents and young adults who had the athetoid pseudobulbar and severe brainstem cerebellar patterns of lesion.

Guo et al. (2000) conducted a case–control study to investigate the relationship between head injury and the APOE genotype and the risk of AD in participants in the MIRAGE project. The study included a total of 2,233 probands who met criteria of probable or definite AD and 14,668 controls (first-degree family members and spouses) who had participated in the MIRAGE project. Head injury was confirmed by using a structured questionnaire, interviews with multiple informants, and a thorough review of medical records. The authors used conditional logistic

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regression techniques to determine the relationship between head injury and the odds of developing AD. Analyses were adjusted for age, sex, and age at onset of AD. The generalized estimating equation was used to examine effects of the APOE genotype and head injury on the odds of AD. The authors found an OR of 4.6 (95% CI, 3.7–5.9) for AD associated with all types of head injury. In a comparison limited to cases and their unaffected spouses, the ORs for AD were 9.9 (95% CI, 6.5–15.1; $p < 0.001$) for TBI with LOC and 3.1 (95% CI, 2.3–4.0) for TBI without LOC. When subjects were compared with controls who were their parents and siblings, the ORs were 4.0 (95% CI, 2.9–5.5) for TBI with LOC and 2.0 (95% CI, 1.5–2.7) for TBI without LOC. The authors reported that head injury without LOC did not significantly increase the risk of AD in spouses (OR, 1.3; 95% CI, 0.4–4.1). The study is limited in that head injury in probands and family members was ascertained with informant interviews without independent confirmation, so there was potential recall bias.

As discussed in Chapter 5, Guskiewicz et al. (2005) studied the association between recurrent concussion and long-term health outcomes, including mild cognitive impairment, AD, and risk of depression in retired professional football players. The authors found no association between recurrent concussion and AD but observed earlier onset of AD in the retired football players than in the general American male population.

Shalat and colleagues (1987) conducted a case–control study to assess risk factors for AD in 98 men who had clinically diagnosed AD and 162 normal controls. Subjects were identified through the Geriatric Research, Education, and Clinical Center and the Edith N. Rogers Memorial Veterans Hospital in Bedford, MA. Controls were selected from a list of Massachusetts registered voters and were matched to cases on sex, age, and region of residence. Information was obtained with mailed questionnaires completed by spouses or next of kin at the same addresses. The authors found excess odds of severe head trauma in the subjects (OR, 2.4; 95% CI, 0.5–11.1).

A meta-analysis of seven case–control studies of AD (including Amaducci et al., 1986; Broe et al., 1990; and Heyman et al., 1984) to assess the interaction of genetic and environmental risk factors, including head injury, was largely supportive of the findings described above. Van Duijn and colleagues (1994) found that "late maternal age at birth and a history of head trauma [were] associated with a statistically significant increase in the risk for AD in the absence of a family history of dementia."

Summary and Conclusions

The committee identified one primary study (Plassman et al., 2000) and nine secondary studies (Schofield et al., 1997; Amaducci et al., 1986; Broe et al., 1990; French et al., 1985; Heyman et al., 1984; Lewin et al., 1979; Guo et al., 2000; Guskiewicz et al., 2005; Shalat et al., 1987) that assessed the relationship between TBI and dementia of the Alzheimer's type. Plassman et al. (2000) investigated the relationship between nonpenetrating TBI and the risk of AD and other dementias in WWII veterans. The authors found that a history of TBI increased the risk of AD (HR, 2.00; 95% CI, 1.03–3.90) and dementia (HR, 2.23; 95% CI, 1.30–3.81). Moderate TBI (HR, 2.32; 95% CI, 1.04–5.17) and severe TBI (HR, 4.51; 95% CI, 1.77–11.47) were both associated with increased risk of AD. Similarly, moderate TBI (HR, 2.39; 95% CI, 1.24–4.58) and severe TBI (HR, 4.48; 95% CI, 2.09–9.63) were both associated with dementia. There was no significant risk of AD (HR, 0.76; 95% CI, 0.18–3.29) or dementia (HR, 1.33; 95%

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CI, 0.51–3.47) in those with mild TBI. Except for the studies of Amaducci et al. (1986) and Broe et al. (1990), the secondary studies found an increased risk of AD after TBI. A meta-analysis of seven case–control studies supported these findings, noting that "a history of head trauma [was] associated with a statistically significant increase in the risk for AD in the absence of a family history of dementia" (Van Duijn et al., 1994).

Taken as a whole, the studies generally found a strong association between moderate or severe TBI and dementia of the Alzheimer's type. Studies suggested an association between mild TBI with LOC and dementia of the Alzheimer's type, but mild TBI without LOC was not found to be strongly associated with dementia of the Alzheimer's type.

The committee concludes, on the basis of its evaluation, that there is sufficient evidence of an association between moderate or severe TBI and dementia of the Alzheimer's type.

The committee concludes, on the basis of its evaluation, that there is limited/suggestive evidence of an association between mild TBI (with LOC) and dementia of the Alzheimer's type.

The committee concludes, on the basis of its evaluation, that there is inadequate/insufficient evidence to determine whether an association exists between mild TBI (without LOC) and dementia of the Alzheimer's type.

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TABLE 7.8 Dementia of the Alzheimer's Type and TBI

Reference	Study Design	Population	Type of TBI: Mild, Moderate, Severe; Blunt, Penetrating, Blast	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
Plassman et al., 2000	Retrospective cohort; review of military hospital records	World War II US Navy or Marines male veterans serving in military in 1944–1945, hospitalized during military service for head injury (n = 548) or unrelated injury (n = 1,228)	Nonpenetrating head injury with LOC, PTA, or skull fracture that resolved within 3 mo of injury Mild: LOC, PTA <30 min, no skull fracture; moderate: LOC, PTA <24 h, and/or skull fracture; severe: LOC, PTA >24 h	AD, other dementias Risk of dementia, including AD, through verification of medical records and three-stage diagnostic procedure: Telephone Interview for Cognitive Status (TICSm), telephone DQ, clinical assessment of AD diagnosed according to NINCDS-ADRDA criteria	AD risk with moderate head injury: HR, 2.32 (95% CI, 1.04–5.17); AD risk with severe head injury: HR, 4.51 (95% CI, 1.77–11.47) Results similar for dementia	Controls matched on education, age	Review of 50-year-old medical records' well-defined head-trauma group

NOTE: AD = Alzheimer disease, ADRDA = Alzheimer's Disease and Related Disorders Association, CI = confidence interval, DQ = dementia questionnaire, HR = hazard ratio, LOC = loss of consciousness, NINCDS = National Institute of Neurological and Communicative Disorders and Stroke, PTA = posttraumatic amnesia, WWII = World War II.

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DEMENTIA PUGILISTICA

Dementia pugilistica (DP) is a neurologic disorder that primarily affects boxers who are exposed to multiple head injuries. Some studies refer to DP as chronic traumatic encephalopathy (CTE) or punch-drunk syndrome. It is commonly associated with declines in mental and physical abilities, such as dementia and parkinsonism. Some authors have described the development of DP along a continuum. Mendez (1995) notes that the spectrum of CTE in professional boxers can range from mild, "subclinical" brain damage to the syndrome of DP. CTE is initially characterized by motor, cognitive, and psychiatric symptoms. Mendez reports that there may be a gradual worsening to middle and late stages of CTE over the course of 7–35 years if boxing exposure continues. The end stage of progressive CTE is DP (Mendez, 1995). In mild cases of DP, the most common symptoms include are slurring dysarthria, gait ataxia, disequilibrium, and headache. Clinical symptoms often occur 10–20 years after retirement from the sport. Neuropsychologic tests are often used to assess cognitive decline associated with DP. Studies of boxers who were thought to have symptoms of DP have found deterioration in tests of memory, information processing and speed, finger-tapping speed, attention and concentration, sequencing abilities, judgment, abstraction, reasoning, planning, and organization (McCrory et al., 2007). More recently, studies have also been done of soccer players since repeated heading may also cause repeated TBI.

The committee focused its evaluation on the primary population that exhibits this effect: boxers. Boxers are typically subjected to repeated blows to the head. As Millspaugh (1937) reported in 1937, "the etiology of dementia pugilistica is trauma, usually repeated frequently and varying from a comparatively insignificant abrasion, contusion or laceration to compound fracture, brain concussion, loss of consciousness, shock, coma, and death." Repeated blows to the head can produce rotational acceleration of the brain, diffuse axonal injury, and other neuropathologic conditions (Mendez, 1995).

The prevalence of DP among boxers is well discussed in the older literature. Martland (1928) was the first to identify "punch-drunk syndrome" in boxers. In 1936, Carroll noted that "there is a clinical syndrome of frequent occurrence among boxers to which they refer as 'punch drunk'." The term dementia pugilistica was coined by Millspaugh in 1937, and in 1949, Critchley introduced the term chronic progressive post-traumatic encephalopathy of boxing. More recently, Mendez (1995) noted that "professional boxers with multiple bouts and repeated head blows are prone to chronic traumatic encephalopathy."

In reviewing the literature on DP in boxers, the committee recognized that there is a considerable difference between amateur boxing and professional boxing in measures to protect against head injury. In amateur boxing, bouts are usually limited to three rounds of 3 minutes each; gloves are typically larger, heavier, and more absorbent than those used by professional boxers (Stewart et al., 1994). Amateur boxers pursue "points" rather than knockout blows to win a match. Also, in1984–1986, additional safety measures were introduced into the sport, including the requirement to use headgear; and matching novice boxers with opponents of similar skill level. Bouts are stopped when boxers are at risk of head injury, and mandatory suspension rules can be used when head injuries are observed (Stewart et al., 1994). Professional boxers are not required to adhere to those safety measures, including the use of headgear. That may partially explain why DP is observed primarily in professional boxers and why findings from studies

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sometimes differ depending on whether the population studied consists of professional boxers or amateur boxers.

The committee did not identify any studies that met the criteria for a primary study, because there was not a clear identification of TBI in the population of boxers, rather participation in boxing or soccer was used as a surrogate measure for TBI. In addition, the severity of head injury and the nature of repeated trauma were unknown.

Secondary Studies

The committee identified six secondary studies that evaluated the relationship between TBI and DP in boxers and soccer players. Four of them are limited by their use of boxing as a proxy for TBI. Another used soccer headings as a proxy for head injury. Some of the studies included subjects under 18 years old. One study was a pathology study of retired boxers to assess cerebral changes characteristic of DP.

Drew and colleagues (1986) assessed neuropsychologic deficits consistent with DP in 19 licensed professional boxers. The 19 boxers were a subset of 87 active licensed professional boxers in an area of California. Initial contact was made with 38 potential participants; 29 agreed to participate, but 10 of them did not show up for testing, and that left 19 participants. The control group consisted of athletes identified through the Fresno Parks and Recreation Department who were active in organized basketball or baseball. The controls were comparable with the boxers in age, race, and education. Exclusion criteria for controls included history of drug abuse, boxing, or head trauma. The boxing history of the boxers was assessed and showed a range in the number of amateur bouts of one to 195 (mean, 52.8; SD, 55.98) and of professional bouts from zero to 37 (mean, 13.7; SD, 13.08). The total of amateur losses and draws ranged from zero to 15 (mean, 5.2; SD, 4.47), and the total of professional losses and draws ranged from zero to 10 (mean, 3.8; SD, 2.88). Both groups were given various subtests of the Quick Neurological Screening Test, the Randt Memory Test, and the Halstead-Reitan Neuropsychological Test Battery. The authors found that boxers demonstrated significantly more deficits than controls in all tests except Seashore Rhythm, Finger Tapping, and Category Test. The boxers also scored worse than controls on all the summary scores of impairment. Of the 19 boxers, 15 scored in the impaired range on the Reitan Impairment Index; only two of the 10 controls scored in this range.

As discussed in Chapter 5, Porter and Fricker (1996) conducted a neuropsychologic assessment of 20 amateur boxers, 16–25, in the six largest boxing clubs in Dublin, Ireland; 20 controls matched on age and socioeconomic status also participated in the study. Each of the amateur boxers was to have competed in a minimum of 40 amateur matches. The boxers were given a battery of neuropsychologic tests by an independent examiner initially in 1992 and again 15–18 months later. The tests included Trail-Making Tests A and B, the Finger Tapping Test (FTT), and the Paired Associate Learning Test. The authors found that the boxers performed significantly better then the controls on Trail-Making Tests A and B, but the control group's scores on the FTT were significantly higher than those of the boxers, and the boxers' scores in the FTT (dominant hand) showed significant deterioration. The authors noted that there was no evidence of neuropsychologic impairment in the boxers compared with the controls, and they found no association between boxing and performance on any of the neuropsychologic tests.

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Porter (2003) conducted a followup study of the same population of 20 amateur boxers and 20 matched controls. Again, the subjects underwent a repeated battery of neuropsychologic tests at 18 months, 4 years, 7 years, and 9 years after an initial assessment. The boxers scored higher than the controls on Trail Making Tests A and B at all time but lower on the FTT at all times except baseline for the dominant hand. The authors found no evidence of neuropsychologic impairment over the 9-year period. In fact, the boxers improved on some of the tests in comparison with the controls.

Roberts (1969) examined 250 ex-professional boxers from a random sample of British boxers who first registered in 1929–1955 and had professional licenses for 3 years. The authors found that 37 exhibited symptoms characteristic of punch-drunk syndrome—evidence of lesions of the central nervous system. Of the 37, four had progressively deteriorated; their symptoms were not thought to be related to the normal aging process. The authors also found that "there were eleven others with evidence of central nervous system disease whose lesions were adequately explicable on the basis of a diagnosis which bore no relation to their boxing careers."

Jordan et al. (1996) assessed chronic encephalopathy in elite soccer players. The subjects included 20 members of the US men's national soccer team training camp and 20 age-matched male elite track athletes. Soccer players were given a questionnaire to assess symptoms of head and neck injuries, number of headings, and number of seasons played on various teams. The authors developed a heading-exposure index to assess cumulative exposure to headings. All subjects also completed a brain MRI scan. Seven soccer players reported a history of headings; five had had complete LOC. Eight runners reported that they had had head injuries; four had complete LOC. The authors found that reported head-injury symptoms, particularly in soccer players, correlated with history of acute head injuries ($r = 0.63$) and noted that the "findings suggest that any evidence of encephalopathy in soccer players relates more to acute head injuries received playing soccer than from repetitive heading."

Corsellis and colleagues (1973) conducted the largest of the pathology studies, examining the brains of 15 retired boxers to assess cerebral changes characteristic of DP. The brains were collected from the Department of Neuropathology and the Institute of Psychiatry at Runwell Hospital, UK. Information about the boxers was collected retrospectively from relatives and friends by a social worker; hospital records were reviewed when available. Of the 15 men, 12 had boxed professionally and three as amateurs. The boxing careers extended from 1900 to 1940. The boxers' age at death ranged from 57 to 91. Autopsies revealed cerebellar damage, cortical damage and other scarring of the brain, substantia nigral degeneration, neurofibrillary tangles in the cerebral cortex and temporal horn areas, and abnormalities of the septum pellucidum.

Summary and Conclusions

The committee identified six secondary studies that assessed the relationship between boxing or repeated heading in soccer and DP. Drew and colleagues (1986) assessed professional boxers and found neuropsychologic deficits consistent with DP. The remaining secondary studies found mixed results. Porter (2003) and Porter and Fricker (1996) conducted a neuropsychologic assessment of 20 amateur boxers, 16–25 years old, in the six largest boxing clubs in Dublin, Ireland, and found no evidence of neuropsychologic impairment in the boxers compared with the controls. Roberts (1969) examined 250 ex-professional boxers from a random sample of British boxers who first registered in 1929–1955 and had professional licenses for 3 years. The authors

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found that 37 exhibited symptoms characteristic of punch-drunk syndrome; of the 37, four had progressively deteriorated, and their symptoms were not thought to be related to the normal aging process; in the others, the authors found no evidence that neuronal degeneration, rather than age, was the cause. Jordan et al. (1996) noted that "any evidence of encephalopathy in soccer players relates more to acute head injuries received playing soccer than from repetitive heading."

Pathologic findings of DP were observed by Corsellis et al. (1973). Findings were consistent with DP in the 15 boxers who were autopsied. The autopsies revealed cerebellar damage, cortical damage, and other scarring of the brain; substantia nigral degeneration; neurofibrillary tangles in the cerebral cortex and temporal horn areas; and abnormalities of the septum pellucidum.

Findings in professional boxers demonstrate an association with the development of DP; pathology study of brains of autopsied boxers also support these findings. The evidence is less clear in amateur boxing and soccer: it is difficult to know the severity, if any, of the head injury experienced. Therefore, the committee cannot draw a conclusion about TBI and DP in general and has limited its conclusions to professional boxers.

The committee concludes, on the basis of its evaluation, that there is sufficient evidence of an association between professional boxing and development of dementia pugilistica.

PARKINSONISM

Parkinsonism is a neurologic condition characterized primarily by hypokinesia, rigidity, tremor, and postural instability. Parkinson disease is the primary underlying cause of parkinsonism although other factors have been associated with it, including exposure to toxicants and other metabolic conditions. PD is a neurodegenerative disorder resulting from a deficiency in dopamine. Symptoms of PD include tremor, rigidity, bradykinesia, and postural instability; these symptoms gradually progress. An important risk factor for PD is age; it affects mainly people over 50 years old. Diagnosis of PD is based on a thorough review of medical history and a neurologic examination. As with AD, pathologic confirmation of the clinical diagnosis of PD was not reported in most of the studies reviewed by the committee, so it limited its conclusions to the evaluation of the relationship between TBI and parkinsonism.

Primary Studies

The committee identified two primary studies that evaluated the association between TBI and parkinsonism (see Table 7-9). Bower and colleagues (2003) evaluated the association between a history of TBI and PD in a case–control study, and Goldman and colleagues (2006) conducted a case–control study of 93 male twin pairs discordant for PD.

Bower and colleagues (2003) examined a history of TBI as a risk factor for PD in a case–control study, using the medical-records–linkage system of the Rochester Epidemiology Project. Included were 196 cases of PD diagnosed in 1976–1995. Each case of PD was matched on age and sex to a general-population control also residing in Olmsted County, MN. TBI (mild, moderate, or severe) was ascertained by a trained nurse abstractor who reviewed the complete

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medical records of cases and controls. A neurologist also abstracted the information from the records, and a second neurologist independently assessed the presence and severity of TBI. The authors defined TBI as a "head injury with evidence of a presumed brain involvement, that is, concussion with loss of consciousness, posttraumatic amnesia, neurologic signs of brain injury, or skull fracture". TBI was defined as severe if there was brain contusion (based on direct observation during surgery or focal neurologic symptoms), intracranial hematoma, or LOC or PTA lasting over 24 hours. TBI was defined as moderate if there was LOC or PTA lasting 30 minutes to 24 hours or a skull fracture. TBI was defined as mild if there was an absence of skull fracture and there was LOC or PTA lasting less than 30 minutes. A history of TBI was significantly more frequent in men with PD (9.9%) than in their matched controls (1.7%) (OR, 6.0; 95% CI, 1.3–26.8). A history of TBI was also greater in all cases of PD than in matched controls (OR, 4.3; 95% CI, 1.2–15.2; p = 0. 02). Mild TBI accompanied only by PTA was not associated with an increased risk of PD. The authors also considered the association between PD and a history of mild TBI with LOC, moderate TBI, or severe TBI and found a significant association (OR, 11.0; 95% CI, 1.4–85.2; p = 0. 02). The authors noted that the "results suggest an association between head trauma and the later development of PD that varies with severity." Possible study limitations include the broad confidence intervals, the potential for underascertainment of mild TBI from medical records alone, and the possibility that patients with more severe TBI might be followed more closely in the medical system, a phenomenon that could lead to an earlier diagnosis of PD.

Goldman and colleagues (2006) conducted a case–control study of 93 male twin pairs discordant for PD that were identified through the National Academy of Sciences WWII veteran twins cohort. After screening for PD in a telephone interview, twins who were thought to be likely PD cases were examined in person by a movement-disorder specialist. PD was diagnosed according to the Core Assessment Program for Intracerebral Transplantations criteria. Probable PD was characterized on the basis of "(1) the presence of at least two of the following signs, at least one of which must be either resting tremor or bradykinesia: resting tremor, cogwheel rigidity, bradykinesia, and postural reflex impairment; (2) no other cause of parkinsonism; (3) no signs of more extensive neurodegeneration indicating atypical parkinsonism; and (4) a clear-cut response to L-dopa, if treated". Possible PD was defined in one of the following ways: "(1) meets definitions 2 through 4 above, but neither bradykinesia nor resting tremor is present; (2) meets definitions 2 through 4 above, but only resting tremor is present; (3) meets definitions 1 through 3 above, but response to L-dopa is unknown; (4) meets all of definitions above, but also has another clinical symptom or sign sometimes, but not always, found in PD (eg, prominent dementia, severe dysautonomia)." Each in-person examination was reviewed independently by a second neurologist. Controls were the unaffected twins. To assess TBI, a structured lifetime–head-injury questionnaire was conducted by telephone. TBI was associated with an increased risk of PD (OR, 3.0; 95% CI, 1.2–7.6). The association between a history of TBI and later PD was stronger for two or more TBIs (OR, 4.3; 95% CI, 0.46–41) than for only one TBI (OR, 3.6; 95% CI, 1.1–12; p for trend = 0.022). The association between head injury and PD was slightly stronger in monozygotic than in dizygotic pairs. The authors also conducted a subanalysis of 18 twin pairs concordant for PD and found that the twin with earlier onset of PD was more likely to have sustained TBI. However, the authors cautioned that the number of subjects in the analysis was small.

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Secondary Study

The committee identified one secondary study of the relationship between TBI and parkinsonism. Taylor and colleagues (1999) conducted a case–control study to assess risk factors for PD. The subjects were 140 patients of the Movement Disorder Center at Boston University Medical Center diagnosed with PD. Each subject was examined by a neurologist. The controls were 147 people—matched on age, sex ratio, and socioeconomic status—were recruited through the PD patient population of the Movement Disorder Center. None of the controls had a diagnosis of PD or met diagnostic criteria for PD. Data were collected on environmental exposure, family history of illness, and comprehensive medical history, including age at onset of PD and at diagnosis, head injury, smoking, vitamin intake, and depression. Head injury was diagnosed if the trauma was "severe enough to cause loss of consciousness, blurred or double vision, dizziness, seizures, or memory loss". Subjects and controls were stratified into birth cohorts in 5-year intervals, and the average age at onset of PD was calculated for each birth cohort. Chi-square tests were used to test differences in ORs; univariate logistic regression was used to calculate ORs for family history. The mean period between age at reported head injury and age at onset of PD was 36.5 years. The authors found that four factors were associated with increased odds of PD: TBI (OR, 6.23; 95% CI, 2.58–15.07), family history of PD (OR, 6.08; 95% CI, 2.35–15.58), family history of tremor (OR, 3.97; 95% CI, 1.17–13.50), and history of depression (OR, 3.01; 95% CI, 1.32–6.88). Possible study limitations include recall bias related to the extensive time between head injury and onset of PD.

Summary and Conclusion

The committee identified two primary studies (Bower et al., 2003; Goldman et al., 2006) and one secondary study (Taylor et al., 1999) that evaluated the association between TBI and parkinsonism. The results of all three suggested an association. Bower and colleagues (2003) conducted a case–control study of PD as related to TBI by using the medical-records–linkage system of the Rochester Epidemiology Project and found that the frequency of head trauma overall was significantly higher in people with PD than in controls. An increased risk was observed in patients with mild TBI and LOC or with more severe TBI. The authors noted that the "results suggest an association between head trauma and the later development of PD that varies with severity." Goldman and colleagues (2006) conducted a case–control study of male twin pairs discordant for PD and found that TBI with LOC or PTA was associated with an increased risk of PD. Taylor et al. (1999) conducted a case–control study to assess risk factors related to PD and found that TBI was associated with an increased risk of PD.

The committee concludes, on the basis of its evaluation, that there is sufficient evidence of an association between moderate or severe TBI and parkinsonism.

The committee concludes, on the basis of its evaluation, that there is limited/suggestive evidence of an association between mild TBI (with LOC) and parkinsonism.

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TABLE 7.9 Parkinsonism and TBI

Reference	Study Design	Population	Type of TBI: Mild, Moderate, Severe; Blunt, Penetrating, Blast	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
Bower et al., 2003	Case-control, derived from REP	196 PD patients living in Olmsted County, MN, with onset 1976–1995	Mild, moderate, severe; included only cases with impairment of consciousness or memory at time of injury	PD, determined by neurologist review of medical records, previously validated method	Any head trauma, OR, 4.3 (95% CI, 1.2–15.2) Severe trauma, OR, 11.0 (95% CI, 1.4–85.2) Mild trauma, no increased risk of PD Men, OR, 6.0 (95% CI, 1.3–26.8) Women, NS Age of onset >71 years, p = 0.02 (no OR because of lack of data on controls)	Matched 1 to 1 on age; separate analyes stratified on age of onset, severity of TBI, family history of PD	Incident cases reviewed, thus avoiding referral bias Broad CI because PD rare People with mild TBI might not have sought medical attention, thus would not be in system; result would be underascertainment of mild TBI; if distributed equally in PD case, controls, bias would be toward finding no effect of mild TBI on risk of PD Patients with significant head trauma might be followed more closely; this would lead to earlier or more frequent diagnosis of PD

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Reference	Study Design	Population	Type of TBI: Mild, Moderate, Severe; Blunt, Penetrating, Blast	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
Goldman et al., 2006	Case control	93 twin pairs ascertained from National Research Council WWII Veteran Twins Cohort	Mild to moderate: head injury with LOC or amnesia	Screened for PD in telephone interview; examined twins with likely PD; PD diagnosed according to CAPIT criteria	OR, 3.8 (95% CI, 1.3–11; p = 0.014); PD risk greater if two or more previous TBIs than if one (p for trend = 0.022) Association stronger in monozygotic twins than in dizygotic twins In subanalysis of 18 pairs concordant for PD, twin with earlier PD onset more likely to have sustained head injury		

NOTE: CAPIT = Core Assessment Program for Intracerebral Transplantations, CI = confidence interval, LOC = loss of consciousness, NS = not significant, OR = odds ratio, PD = Parkinson's disease, REP = Rochester Epidemiology Project, TBI = traumatic brain injury, WWII = World War II.

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MULTIPLE SCLEROSIS

MS, a chronic nervous system disorder caused by progressive deterioration of the myelin sheath, is characterized by such symptoms as muscle weakness, visual disturbances, coordination and balance problems, and cognitive and memory problems. Symptoms can range from mild to severe; severe symptoms can include an inability to speak and paralysis. The disease is more likely to affect women, and onset typically occurs at the ages of 20–40. As of 2002, the prevalence of MS in the United States was estimated to be 85/100,000 population (Noonan et al., 2002).

Primary Study

The committee identified one primary study of the relationship between TBI and MS (see Table 7-10). Goldacre and colleagues (2006) conducted a population-based record-linkage study to investigate the risk of MS after head injury. To ascertain those with and those without TBI, data were collected from the Oxford record-linkage study on hospital admissions for TBI in January 1963–March 1999. To ascertain later MS, those data were linked to death data and to hospital admissions for MS in the same period. The cohort with TBI (110,993) was compiled by using information on patients admitted with mild, moderate, or severe head injury (as defined by ICD-9 codes 850–854). The reference group (534,600) was selected by using medical records of people admitted for a wide array of health conditions in the same period. Excluded from the study were those with MS recorded before or at admission and those 85 years old or older at the time of TBI. Rates of later MS were calculated and standardized by age (in 5-year age groups), sex, calendar year of first recorded admission, and area of residence. The authors found that there was no difference in the risk of MS between people with and people without TBI (RR, 1.1; 95% CI, 0.88–1.36). When the time since TBI was examined, there was no significant increase in the risk of MS after either short or long periods. Nor was the risk of MS increased after head injury with a hospital stay of less than 2 days (RR, 1.1; 95% CI, 0.71–1.57), of 2 days or more (RR, 1.0; 95% CI, 0.68–1.45), or of 7 days or more (RR, 1.3; 95% CI, 0.64–2.34). The study has limitations with respect to the identification of mild TBI, but not moderate or severe TBI; only people hospitalized for mild TBI would have been identified.

Secondary Study

The committee identified one secondary study that assessed the relationship between TBI and onset of MS. Kurland (1994) used population data from the Rochester Epidemiology Project (discussed further in Chapter 5) to assess the relationship between TBI and MS. The author identified all the cases of MS diagnosed in the local population of Olmsted County, MN, in 1905–1991. Also identified were people with TBI (819) and lumbar disk surgery (942). Head trauma was defined as TBI with evidence of skull fracture and/or LOC or PTA. The author found no correlation between onset or exacerbation of MS and TBI or lumbar disk surgery.

Summary and Conclusion

The committee identified one primary study and one secondary study of the relationship between TBI and MS. The primary study (Goldacre et al., 2006) found no association or

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increased risk of MS after head injury. Similarly, the secondary study (Kurland, 1994) found no correlation between onset or exacerbation of MS and head injury.

The committee concludes, on the basis of its evaluation, that there is inadequate/insufficient evidence to determine whether an association exists between TBI and the development of MS.

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TABLE 7.10 Multiple Sclerosis and TBI

Reference	Study Design	Population	Type of TBI: Mild, Moderate, Severe; Blunt, Penetrating, Blast	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
Goldacre et al., 2006	Cohort (population-based record-linkage study) derived from Oxford Record Linkage Study	110,993 people with report of head injury (ICD-9 codes 850-854); ICD-9 534, 600 in reference group; identified January 1, 1963–March 31, 1999	Mild, moderate, severe as determined by length of hospital stay at time of injury (mild, <2 days; moderate, 2–7 days; severe, >7 days)	MS and head injury as identified through hospitalizations or deaths in same period (1963–1999)	OR, 1.1 (95% CI, 0.88–1.36; p = 0.42); mean followup, 16.7 years	Standardized by age (in 5-year groups), sex, calendar year of first recorded admission, district of residence	Takes into account only those hospitalized with MS or identified at death Mild TBI may be underidentified inasmuch as all TBI identified during hospitalization No adjustments for other potential risk factors Limitation is mixed age group; ages 0–65+ years included Strengths of study include head injury, MS diagnoses made independently, so recall bias avoided Geographically defined but otherwise unselected population Analysis of long- and short-term risk of MS after TBI

NOTE: CI = confidence interval, ICD = International Classification of Diseases, MS = multiple sclerosis, OR = odds ratio, TBI = traumatic brain injury.

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AMYOTROPHIC LATERAL SCLEROSIS

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is a neuromuscular disease that causes degeneration of motor neurons in the cerebral motor cortex, the brainstem, and the spinal cord, which leads to muscle weakness and atrophy. In the final stages of the disease, the muscles responsible for breathing are disrupted; patients often die from respiratory failure. It is estimated that 5–10% of ALS cases are inherited, and the causes of the remaining cases are unknown. ALS affects 20,000–30,000 people in the United States and is more prevalent in men than in women. The risk of the disease increases with age (IOM, 2006).

The committee identified no primary studies and few secondary studies of the relationship between TBI and ALS, but it recognized the importance of evaluating the literature for this outcome because there has been a concern about a relationship of the disease to military service (IOM, 2006).

Secondary Studies

The committee identified two secondary studies related to ALS. Chen et al. (2007) conducted a case–control study of 110 ALS cases at two major referral centers in New England. The patients, recruited in 1993–1996, received a diagnosis of ALS according to the standard criteria of the World Federation of Neurology and met the following criteria: received the diagnosis within the previous 2 years, lived in New England for half the year, spoke English, and were mentally competent. The control population consisted of 270 people without a diagnosis of dementia, parkinsonism, neuropathy, postpoliomyelitis syndrome, ALS, or other motor neuron diseases. Controls were frequency-matched to cases on age, sex, and telephone area code. Information on subjects and controls was collected by using a structured questionnaire administered by trained interviewers. To determine whether people had TBI, they were asked whether they had ever been injured so severely that they required medical attention and, if so, were then asked for details about the injury to identify TBI. The authors found that a history of TBI was associated with a higher risk of ALS. Compared with those who did not have TBI, there were significantly higher odds of ALS in patients with more than one TBI (OR, 3.1; 95% CI, 1.2–8.1) and in patients who had TBI during the preceding 10 years (OR, 3.2; 95% CI, 1.0–10.2). In patients who had multiple TBIs in the preceding 10 years, the risk of ALS was more than 11 (95% CI, 1.1–114.3), but the number of cases was small.

Kurtze and Beebe (1980) conducted a case–control study to assess risk factors for ALS. They identified 504 WWII veterans whose deaths were attributed to ALS during 1963–1967. The control population consisted of 504 men matched to subjects on age, entry into military service, and branch of service. To assess the validity of the ALS diagnosis, the authors reviewed hospital records and identified 37 representative deaths attributed to ALS; 36 were found to have definite ALS. The records were also reviewed for information about physical condition on entry into the service and other medical issues, including diseases and injuries. There were eight intracranial injuries in ALS subjects compared with two in controls. The authors found that "men dying of ALS more often had a history of injury 15 or more years before death than did the controls during the same period."

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Summary and Conclusion

The committee did not find any studies that met the criteria for a primary study of TBI and ALS (see Chapter 4); however, it did identify two secondary studies. Chen and colleagues (2007) found that ever having experienced a TBI was not significantly associated with a higher ALS risk. However, compared with those who did not have TBI, there were significantly higher odds of ALS risk for patients with more than one TBI (OR, 3.1; 95% CI, 1.2–8.1) and patients who had TBI during the preceding 10 years (OR, 3.2; 95% CI, 1.0–10.2). For patients with multiple head injuries in the preceding 10 years, the risk of ALS was more than 11 -fold. Kurtze and Beebe (1980) found a higher frequency of intracranial injury in ALS subjects than in controls and stated that "men dying of ALS more often had a history of injury 15 or more years before death than did the controls during the same period." The secondary studies generally found higher rates of ALS in the head-injured, but no studies that met the criteria of a primary study were identified.

The committee concludes, on the basis of its evaluation, that there is inadequate/insufficient evidence to determine whether an association exists TBI and the development of ALS.

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8

PSYCHIATRIC OUTCOMES

Psychiatric disorders after traumatic brain injury (TBI) have been well documented. Rogers and Read (2007) note that survivors of brain injury are at particularly increased risk for depression, generalized anxiety disorder, and posttraumatic stress disorder (PTSD), although the etiology is unclear. They further note that psychiatric sequelae are often among the most disabling consequences of a TBI and can adversely affect recovery and psychosocial outcome.

As advances in neuroscience have begun to elucidate the pathophysiology of psychiatric disorders, there is progress toward delineating the specific regional brain structures, functions, and chemistry underlying the conditions (Drevets, 2001; Rauch et al., 2006). The *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition (DSM-IV), which is considered the gold standard for psychiatric diagnosis, explicitly distinguishes between psychiatric disorders that emerge in a primary fashion (for example, major depressive disorder) and those attributable to a specific medical cause, such as an endocrine disturbance, stroke, or TBI (for example, mood disorder due to a general medical condition).

Taylor and Jung (1998) postulate that a person's decreased ability to function at work and at home after a TBI leads to psychologic distress that in turn leads to the development of mood disorders with greater frequency than in the general population. In such cases of nonspecific effects of psychologic stress, a primary psychiatric diagnosis in accordance with DSM-IV would be appropriate. In contrast, if the psychiatric condition were deemed to be a direct consequence of the TBI because of disruption of brain function—for example, as is believed to occur when stroke affects specific brain distributions (Spalletta et al., 2006)—the diagnosis of mood disorder due to a general medical condition might be more appropriate. In addition to the possibility that TBI leads to psychiatric sequelae through nonspecific psychologic factors or through more specific brain-injury–related factors, there is evidence that prior psychiatric illness may predispose to TBI, which in turn could increase the risk of recurrence or exacerbation of previous psychiatric conditions (Fann et al., 2002). Thus, given the uncertainty regarding the mechanisms that link TBI and psychiatric diagnoses, we have chosen to use the terminology of primary psychiatric disorders, as has been the custom in the TBI literature on psychiatric outcomes.

The committee reviewed approximately 350 studies of mood and anxiety disorders and other psychiatric outcomes after brain injury. Few studies, however, met the committee's criteria for a primary study.

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MOOD DISORDERS

Mood disorders are a cluster of mental disorders that are characterized by mood swings or an abnormally depressed (low) or manic (elevated or irritable) mood. The most common mood disorder is major depression; others include bipolar disorder (or manic-depressive disorder), cyclothymia, and dysthymia (United States Department of Health and Human Services, 2006). Major depression is characterized by persistent feelings of sadness accompanied by several symptoms related to changes in appetite or sleeping patterns, loss of interest in activities, fatigue, inability to concentrate, and hopelessness or suicidal thoughts. Bipolar disorder is characterized by at least one manic episode and often by recurring episodes of mood disturbance, including both depressed and manic episodes. Bipolar disorder typically begins in a person's middle twenties, tends to appear in families, and is a lifelong disorder. There are few published data on an association of TBI with bipolar disorder. Suicidal behavior is one of the most serious consequences of mood disorders and may consist of suicidal ideation (thoughts), suicide attempts, or completed suicide; suicide is discussed in the next section of this chapter.

Primary Studies

The committee identified four primary studies that examined an association between TBI and mood disorders. Fann et al. (2004) conducted a prospective cohort study to determine the risk of psychiatric illness after TBI. Patients were drawn from a health maintenance organization, Group Health Cooperative of Puget Sound, and received care in its facilities in six different counties in Washington. Computerized records of 939 health-plan members, 15 years old or older who had a diagnosis of a TBI in 1993 were available. Each patient was matched on sex, age, and reference date to three randomly selected unexposed health-plan members. TBI was ascertained in an emergency room, hospital or outpatient clinic, and severity of TBI was established by using the Centers for Disease Control and Prevention criteria. Psychiatric illnesses were ascertained by using the presence of psychiatric diagnoses, filling of prescriptions for psychiatric medications, and utilization of psychiatric services. In the first year after a moderate to severe TBI, 49% of the patients had evidence of psychiatric illnesses compared with 34% in the mild-TBI group and 18% in the comparison group; this reflected a significantly increasing risk of psychiatric illness with severity of TBI. The authors also found the risk of psychiatric illness to be greatest in the 6-12 months after the TBI in analyses that separately considered whether or not psychiatric illness had occurred in the year before injury. In patients without psychiatric illness in the year before injury, there was a 4-fold increased risk for developing a psychiatric disorder in the 6 months after a moderate to severe TBI (95% confidence interval [CI], 2.4–6.8) and a 2.8-fold increased risk after a mild TBI (95% CI, 2.1–3.7) compared with the risk in patients without a TBI. In patients with prior psychiatric illness, the corresponding increases in risk of psychiatric illness were factors of 2.1 (95% CI, 1.3–3.3) and 1.6 (95% CI, 1.2–2.2), respectively. The limitations of the study include the possible lack of precision in TBI exposure measurement, uncertainty regarding past psychiatric diagnosis occurring more than 1 year before ascertainment, and possible confounding by socioeconomic status.

Holsinger et al. (2002) examined the association between TBI and lifetime and current depression in a nested case–control study of World War II veterans. Cases were World War II veterans who had been hospitalized for TBI in 1944–1945 and controls were veterans who had been hospitalized during the same period with either pneumonia or serious laceration or other

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wounds but without TBI. Veterans were identified 50 years after the war on the basis of the diagnosis reported on their "F-cards" in their medical records. Of the 3,460 veterans with reported head injuries (combat-related and noncombat-related), 1,422 met the authors' criteria for TBI—documented TBI in a military record; occurrence during military service; produced loss of consciousness (LOC), posttraumatic amnesia (PTA), or nondepressed skull facture; failure to penetrate the dura mater; and lack of significant cognitive impairment or neurological sequelae more than 3 months after the trauma—and 520 were included in the study. TBI was categorized as mild, moderate, or severe on the basis of the duration of LOC or PTA. Motor-vehicle crashes (26%), falls (19%); and blast concussions (17%) were the leading causes of head injuries. Among the 4,022 potential controls, 1,198 were included in the study.

A lifetime history of depression was assessed on the basis of a structured telephone interview with the veteran or his proxy; participants who responded affirmatively to any of three questions regarding mood also were given a modified version of the Diagnostic Interview Schedule for depression to decide on a DSM-IV diagnosis of major depression. The lifetime odds of major depression was significantly increased in veterans with TBI compared with controls (odds ratio [OR], 1.54, 95% CI, 1.17–2.04). Current major depression was also significantly increased in veterans with TBI (OR, 1.63, 95% CI, 1.07–2.50). The odds of lifetime depression also varied with TBI severity with ORs of 1.99 (95% CI, 1.11–3.57) for severe TBI, 1.40 (95% CI, 0.97–1.83) for moderate TBI, and 1.49 (95% CI, 0.96–2.31) for mild TBI. Alcohol abuse, myocardial infarction, and cerebrovascular accident did not appear to influence the association between TBI and lifetime risk of major depression. However, the odds did increase with age: ORs were 0.81 (95% CI, 0.45–1.43) for men aged 65–69 years old, 1.45 (95% CI, 1.07–1.97) for men 70–74 years old, 2.61 (95% CI, 1.58–4.30) for men 75–79 years old, and 5.95 (95% CI, 2.05–17.23) for men 80 years old and older were. One important limitation of this study was the failure to specifically ascertain the presence of major depression before TBI.

Jorge et al. (2004) assessed the presence of comorbid psychiatric disorders in 91 consecutive patients with closed TBI and a comparison group of 27 patients with multiple trauma but without evidence of central nervous system injury who were admitted at injury to two Iowa medical facilities. Patients with peripheral nerve injuries or spinal-cord injuries were excluded. All included patients were assessed at 3, 6, and 12 months after injury. A modified version of the Present State Examination and the Structured Clinical Interview for DSM-IV diagnoses were used to make a DSM-IV diagnosis of mood and anxiety disorder. The severity of symptoms of depression and anxiety was assessed with the Hamilton Depression Rating Scale and the Hamilton Anxiety Scale; aggressive behavior was assessed with the Overt Aggression Scale. Neuroimaging was done with computed tomography scans or magnetic resonance imaging, and a neuropsychologic assessment was conducted at 3 months. Of the 91 TBI patients, 47 (51.6%) developed a mood disorder in the 12 months after their injury, 30 (33%) of whom had major depressive disorder. There was no significant between-group difference with respect to prior history of depression or anxiety disorders. Mood disorder was statistically significantly more common in the TBI group than in the comparison group during the first year after injury (51.6% vs 22.2%, $p = 0.006$). Of the patients who met DSM-IV criteria for mood disorder, 30 of the TBI patients presented with major depression compared with controls ($p = 0.008$).

The authors compared the 30 TBI patients who had major depressive disorder with the 44 TBI patients who did not develop any mood disorder in the 12 months after injury. Of the 30 TBI patients with major depression, 23 (76.7%) also met the criteria for an anxiety disorder compared

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with nine (20.5%) of the 44 TBI patients without major depression ($p < 0.001$). Of the 23 patients with both major depression and an anxiety disorder, 14 had generalized anxiety features, two had generalized anxiety and panic attacks, and seven met the criteria for PTSD. Significant aggressive behavior was seen in 17 (56.7%) of the 30 patients with TBI and major depression compared with 10 (22.7%) of the 44 TBI controls ($p = 0.003$). Half the 30 patients with TBI and major depression received the diagnosis at their initial evaluation, and an additional nine patients received the diagnosis at the 3-month follow-up. There were no significant differences between TBI patients with and without major depression in demographic variables or the use of alcohol or other drugs. Those with TBI and major depression had a significantly higher frequency of a personal history of mood disorders ($p = 0.01$) and anxiety disorders ($p = 0.05$).

A recent study by Hoge et al. (2008) examined consequences of mild TBI in US soldiers that saw a high level of combat during a year long deployment in Iraq. About 3-4 months after return from Iraq, soldiers were sent a questionnaire covering injury, combat intensity, physical symptoms, major depression, and PTSD. Soldiers were considered to have mild TBI if they answered yes to any of three questions—about losing consciousness, being dazed or confused, or not recalling the injury. The answers to those questions were used to form two subgroups within the mild-TBI group to determine whether LOC was a stronger predictor (that is, one that had LOC and one that had dazing or confusion or did not recall the injury—the second made up the altered-mental-status group). The final samples were 124 with mild TBI and LOC, 260 with mild TBI and altered mental status, 435 with other injury, and 1,706 with no injury. PTSD was present in 43.9% with LOC, in 27.3% with altered mental status, in16.2% with other injury, and 9.1% without injury ($p < 0.001$). Major depression was associated with LOC more than with other injury (22.9% vs 6.6%, $p < 0.001$) but was not associated with altered mental status more than with other injury (8.4% vs 6.6%, $p = 0.39$). Limitations of this study included a failure to control analyses for major depression before TBI. Furthermore, groups were not well matched for combat intensity. Finally, it is unclear how one could effectively distinguish between a history of LOC or altered mental status attributable to TBI and similar phenomena attributable to dissociation[4] in the face of emotional trauma.

Secondary Studies

The committee identified five secondary studies that looked at the association between TBI and mood disorders, specifically, depression. Limitations of these studies include the self-reported diagnosis of TBI and retrospective assessment of mood disorders.

Vanderploeg et al. (2007) conducted a cross-sectional study of the long-term psychiatric, neurologic, and psychosocial outcomes associated with self-reported mild TBI. A subsample of 4,384 veterans was categorized into three groups: no motor-vehicle accident and no TBI (normal control, n = 3,214); injured in a motor-vehicle accident but no TBI (motor-vehicle accident control; n = 539); and TBI with altered consciousness (mild-TBI group; n = 254). Results indicate that the mild-TBI group had a higher frequency of depression than the normal control group (OR, 1.77, 95% CI, 1.13–2.78). The mild-TBI group also had a higher frequency of prior depression than the normal control group, but the adjusted OR was virtually identical (1.78; 95%

[4]Dissociation is a mental state in which a person's thoughts, emotions, or memories are compartmentalized, usually in response to a traumatic event. Some dissociative disorders include psychogenic amnesia, psychogenic fugue, and multiple personality.

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CI, 1.06–3.00) when the analysis was restricted to those who had no prior history of depression. Three other secondary studies also found that depression was associated with TBI (Masson, 1996; Hibbard, 1998, Deb, 1999). In contrast, Malec et al. (2007) examined 51 patients who had moderate to severe TBI, 42 patients who had mild TBI, and 42 controls who had orthopedic injuries and found no difference in depression rates among the three groups.

Summary and Conclusion

The committee reviewed four primary and five secondary studies of mood disorders—major depression—and findings were consistent. The preponderance of studies found that groups with TBI (mild, moderate, or severe) had higher rates of major depression 6 months or longer after TBI than did appropriate comparison groups (including non-TBI injured controls). Three studies (Fann et al., 2004; Jorge et al., 2004; Vanderploeg et al., 2007) provided some control for differences in depression before TBI; all three provided data suggesting that the observed association between TBI and major depression could not be explained by prior depression. Nevertheless, it should be noted that the available data suggest that prior mood disorder may predispose to TBI (Fann et al., 2002; Vassallo et al., 2007) and that post-TBI major depression is more frequent in people who had major depression before TBI than in people who did not (Fann et al., 2004).

In contrast to depression, there are few studies on the relationship between mania or bipolar disorder and TBI (Koponen et al., 2002; Sagduyu, 2002; Silver et al., 2001). Koponen et al. (2002) and Silver et al. (2001) reported a prevalence rate of 1.7% and 1.6%, respectively, of TBI patients who met criteria for bipolar disorder. They concluded that the prevalence did not differ significantly that found in control populations. Sagduyu (2002) examined 535 patients who had bipolar disorder. Of the 126 patients who reported a history of mild TBI, 72 reported symptoms of bipolar disorder prior before the injury, and 54 reported symptoms after the injury. Those studies do not provide consistent or compelling evidence regarding an association between TBI and mania or bipolar disorder.

The committee concludes, on the basis of its evaluation, that there is sufficient evidence of an association between TBI and depression.

The committee concludes, on the basis of its evaluation, that there is inadequate/insufficient evidence to determine whether an association exists between TBI and mania or bipolar disorder.

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TABLE 8.1 Psychologic Outcomes—Mood-Disorder Studies

Reference	Study Design	Population	Type of TBI	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
Fann et al., 2004	Prospective cohort	939 HMO enrollees (479 women, 460 men) with diagnosis of TBI in 1993 enrolled in health plan for at least 1 year before injury, 3 to 1 match with health-plan controls; cases, controls followed for 3 years after enrollment in study	Severity dichotomized with CDC categorization criteria into mild 803). moderate to severe (136); injury identified with ICD-9-CM categories, codes (fracture of vault base of skull; other, unqualified, multiple fractures of skull; intracranial injury)	Psychiatric illness determined with three major indicators: ICD-9-CM codes, prescriptions, use of psychiatric service year before TBI, 1–12, 13–24, 25–36 mo after injury; affective disorders included depression, anxiety	Increased rates of psychiatric illness in year after TBI (49% in moderate to severe, 34% in mild, 18% in non-TBI comparisons) TBI associated with higher risk of any psychiatric illness 6 mo after trauma in subjects with or without prior psychiatric illness: No prior psychiatric illness ($p < 0.001$): mild TBI, RR, 2.8 (95% CI, 2.1–3.7); moderate to severe TBI, RR, 4.0 (95% CI, 2.4–6.8) Prior psychiatric illness (p , 0.005): mild TBI, RR, 1.6 (95% CI, 1.2–2.0); moderate to severe TBI, RR, 2.1 (95% CI, 1.3–3.3) Subjects with mild TBI showed chronic likelihood of psychiatric illness	Age, sex, TBI reference date, logarithm of costs in year before reference date, comorbid injuries	Limitation: control group is general HMO population, not an injury population

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Reference	Study Design	Population	Type of TBI	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
					even in absence of prior psychiatric problems Affective disorders fairly common in TBI group with no prior psychiatric illness, particularly in persons who had mild TBI 1–6 mo: mild TBI, RR, 2.7 (95% CI, 1.5–4.8); moderate to severe TBI, RR, 1.0 (95% CI, 0.1–7.6) 7–12 mo: mild TBI, RR, 2.2 (95% CI, 1.4–3.6); moderate to severe TBI, RR, 4.6 (95% CI, 1.8–11.7) 13–18 mo: mild TBI, RR, 1.9 (95% CI, 1.3–2.6); moderate to severe TBI, RR, 2.2 (95% CI, 1.0–4.9) 19–24 mo: mild TBI, RR, 1.6 (95% CI, 1.2–2.1); moderate to severe TBI, RR,		

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Reference	Study Design	Population	Type of TBI	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
					1.1 (95% CI, 0.4–3.0)		
Holsinger et al., 2002	Population-based retrospective cohort	520 head injured male veterans who were hospitalized for head injury, 1,198 non-head injured WWII male veterans hospitalized with pneumonia or laceration, puncture, or incision wounds; all were on active duty during 1944–1945 in Navy or Marine Corps and were followed at 50 years after injury	Closed head injuries: mild, moderate, severe that (1) was documented in military medical records; (2) occurred during military service; (3) produced LOC, PTA, or nondepressed skull fracture; (4) did not penetrate dura mater; (5) did not result in significant cognitive impairment or neurologic sequelae 3 mo after injury Head-injury severity: mild, LOC or PTA for <30 min; moderate, LOC or PTA 30 min–24 h and/or skull fracture; severe, LOC or PTA 24 h or more	Depressive illness ascertained withmodified DIS for DSM-IV	Lifetime prevalence of depression: head injured, 18.5%; non-head injured, 13.4%; OR, 1.54 (95% CI, 1.17–2.04) Lifetime risk of depression increased with severity of head injury: severe, OR, 1.99 (95% CI, 1.11–3.57); moderate, OR, 1.40 (95% CI, 0.97–2.03); mild, OR, 1.49 (95% CI, 0.96–2.31)	Age, education, history of alcohol abuse, myocardial infraction, cerebrovascular accident	Only male veterans used in study; limited information on age at onset of depression, but it is unlikely that there was history of major depression at time of enlistment Excluded penetrating TBI

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Reference	Study Design	Population	Type of TBI	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
			Sources of head injuries: MV A (26%), blast concussion (17%), fights with peers (7%), falls (19%), sports injuries, including boxing (12%), miscellaneous other wartime happenings (19%)				
Jorge et al., 2004	Cohort	91 consecutive patients with TBI but without spinal-cord injury compared with 27 injured patients without TBI also consecutively admitted into two university hospitals and followed up at 3, 6, 12 mo after trauma	Closed head injury (mild, moderate, severe) Severe TBI: GCS, 3–8; moderate TBI: GCS 9–12 or GCS 13–15 with intracranial surgical procedures or focal lesions greater than 15 mL; mild TBI: GCS 13–15 without surgery or major focal lesions	Major depression associated with anxiety symptoms, Present State Examination, SCID clinical, neuropsychologic, brain-imaging variables	Mood disorders, major depressive disorders significantly more frequent in TBI patients than in patients without brain injuries: after TBI, 47 (51.6%) developed mood disorder compared with six controls (22.2%) group (p , 0.006); major depressive disorder occurred in 30 TBI patients (33%) vs two non-TBI injured (7.4%) (p , 0.008) History of past	None	

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Reference	Study Design	Population	Type of TBI	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
					depression more common in patients with TBI and depression than in those with other injury and depression (36.7% vs 11.4%; $p < 0.01$); similarly, history of past anxiety more common in patients with TBI and depression than in those with other injury and depression (20% vs 4.6%; $p < 0.05$) Major depression significantly associated with comorbid anxiety disorder (76.7% vs 20.4%; $p < 0.001$) and decreased frontal brain volume and left frontal gray matter in first year after injury		

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Reference	Study Design	Population	Type of TBI	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
Hoge et al., 2008	Cohort	Anonymous survey of 4,618 soldiers, of whom 2,714 (59%) completed questionnaire; of 2,714, 149 excluded because of missing data, 40 because they had head injury without LOC Remaining 2,525 US Army soldiers responded 3–4 mo after return from 1-year Iraqi deployment	Mild 124 (4.9%) with LOC 260 (10.3%) with altered mental status (such as dazed or confused) 435 (17.2%) with other injuries	PTSD	Of 124 with LOC, 43.9% met criteria for PTSD compared with 27.3% of those reporting altered mental status, 16.2% with injuries, and 9.1% with no injury Soldiers with mild TBI and LOC more likely to report poor general health, missed workdays, more doctor visits, higher numbers of outcomes or symptoms	95% males; 55.5% under 30 years old; 47.5% junior enlisted rank	After adjustment for PTSD and depression, mild TBI no longer significantly associated with physical health outcomes or symptoms except headache

NOTE: CDC = Centers for Disease Control and Prevention, CI = confidence interval, DIS = Diagnostic Interview Schedule, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, GCS = Glasgow Coma Scale, HMO = health-maintenance organization, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, LOC = loss of consciousness, PTA = posttraumatic amnesia, SCID = Structured Clinical Interview for DSM-IV diagnoses, TBI = traumatic brain injury, WWII = World War II.

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SUICIDE

Suicidal behavior is one of the most serious consequences of mood disorders and may consist of suicidal ideation (thoughts), suicide attempts, and/or completed suicide. It is often associated with psychological conditions such as difficulty of coping with depression or other mental disorders. It is the 11th-most common cause of death in the United States (Medline Plus, 2008); in the Western world, females attempt suicide more frequently than males, but males die more often than females. Few studies have examined the association between TBI and suicide; they are summarized below.

Primary Studies

The committee reviewed two primary studies of the association between TBI and suicide. In a population-based study, Teasdale and Engberg (2001) followed a group of patients who were admitted to a hospital with either a concussion (n = 126,114), a cranial fracture (n = 7,560), or a cerebral contusion or traumatic intracranial hemorrhage (n = 11,766). The groups were identified from all hospital admissions in 1979–1993 in the database of the Danish National Bureau of Health; patients younger than 15 years old and those who died in the hospital or within a month after discharge were excluded. Patients identified on the basis of hospital admissions were compared with the national register of deaths. At the end of 1993, there were 895 recorded suicide deaths: 750 (0.59%) among those with concussions, 46 (0.61%) among those with cranial fractures, and 99 (0.84%) among those with cerebral lesions. More than 68% of all suicides occurred in men and had a median time from injury or lesion to suicide of 3–3.5 years regardless of diagnosis. The higher percentage of completed suicide in males than in females is consistent with the finding that males tend to use more lethal means (such as firearms) than females (CDC, 2008). The standardized mortality ratios (SMR) were statistically significantly increased for all three diagnoses of concussion, fracture, and lesion in both men and women (3.0, 2.7, and 4.1, respectively). Patients who had comorbid substance use had an increased suicide rates in all diagnosis groups. The authors conclude that concomitant risk factors (such as psychiatric illness and psychosocial disadvantage) might predispose to completed suicide in the mild-TBI group. They suggested that the physical, psychologic, and social consequences of more serious TBI pose a greater risk of suicide.

Of 7,000 consecutive patients who had been admitted to a hospital in Oxford, England, between 10–24 years previously, Lewin et al. (1979) studied 291 patients who had been amnesic or unconscious for a week or longer as a result of a TBI. To increase the number of severe-TBI patients, they included 64 selected patients from other sources. Each patient underwent a neurologic examination, and 217 were given a selected series of tests of cognitive function. The cause of death of 75 of the patients with severe TBI who had recovered sufficiently to leave the hospital and walk unassisted was compared with the 1960 death rates in a population of similar sized in England and Wales. Three of the TBI patients died of suicide compared with one in the general population (SMR, 3—not significant).

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Secondary Studies

Shavelle et al. (2001) studied the occurrence of suicide in 168,461 severely disabled individuals who had received services from the California Department of Development Services in 1988–1997. From that group, they selected 2,320 who had a disability resulting from a motor-vehicle accident or cranial injury, were more than 10 years old, and had survived 12 months after injury. Termination of followup was defined as date of death, the end of the study in 1997, or 3 years after the last Client Development Evaluation Report; the latter was to minimize bias in connection with subjects who may have left California during the study period. Mortality information was obtained from computer tapes of state death certificates that included the International Classification of Diseases (ICD) codes for cause of death. During the study period, 119 subjects died. During the previous 5 years, 3% of the 2,320 people with long-term cognitive or communication disability had attempted suicide, including 4% of the 1,107 with the most ambulation; whether this tendency existed before the injury could not be determined. Two people committed suicide during the study period, for an SMR of 1.0; the authors reported that neither of the two persons who completed suicide appeared to have attempted suicide previously.

Simpson and Tate (2002) recruited 172 consecutive outpatients with TBI over a 24-month period at the Brain Injury Rehabilitation Unit of the Liverpool Hospital in Sydney, Australia. All patients were 16–65 years old, had sustained their injuries at least 12 months earlier, and were able to able to respond to questions in English. It was possible to categorize TBI severity in 94 patients for whom a Glasgow Coma Scale (GCS) was available; TBI was mild in 21 patients, moderate in 20, and severe in 53; 76% of the patients had closed head injuries. The Beck Hopelessness Scale and the Beck Scale for Suicide Ideation (BSS) were administered, and the patients were interviewed about alcohol abuse, drug use, and emotional and psychiatric disturbance before and after injury. Moderate to severe hopelessness was seen in 35% of the patients, and 23% reported clinically significant suicide ideation within the previous 7 days; neither score correlated with age at injury, TBI severity, or time after injury. Of the 94 patients, 54 completed the BSS items indicative of suicide ideation, and 28 scored high enough to be considered "clinical." Postinjury suicide attempts were seen in 30 (17.4%) of the 172 patients over a mean period of 5 years, and 26% of all patients attempted suicide at least once in their lifetime; however, only three made attempts both before and after injury. There were no correlations between age, level of hopelessness, and suicide ideation, although significantly more men attempted suicide than would be expected on basis of general population rates ($p < 0.005$). A limitation of this study is the lack of a control group.

Summary and Conclusion

The committee reviewed two primary and two secondary studies of suicide, and findings were consistent among studies, although not all the studies found a statistically significant association between TBI and suicide. The findings are consistent with an association between TBI and major depression. However, the study by Simpson et al. (2002) did not report correlations of TBI with level of hopelessness, suicide ideation, or other concomitant risk factors (such as psychiatric illness).

The committee concludes, on the basis of its evaluation, that there is limited/suggestive evidence of an association between TBI and completed suicide.

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The committee concludes, on the basis of its evaluation, that there is inadequate/insufficient evidence to determine whether an association exists between TBI and attempted suicide.

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TABLE 8-2 TBI and Suicide

Reference	Study Design	Population	Type of TBI	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
Lewin et al., 1979	Retrospective cohort	Consecutive series of 7,000 patients with head injuries admitted into John Radcliffe Infirmary, Oxford, 10–24 years earlier (1955–1969), of whom 479 were amnesic or unconscious >1week Additional selected series: 64 cases unconscious >1mo admitted into this or other facility 3–25 years earlier (including 24 from first set) Causes of death in 78 patients discharged from initial hospitalization alive were compared with causes of death in general population of England and Wales in 1960 (not age- or sex-adjusted)	Severe, in mostly closed, but complicated by compression or penetration (traumatic or surgical for internal decompression) in 77 and 14 of 331 survivors	Vital status; for 178 (consecutive series), 28 (selected series) who died, cause of death; for 331 survivors, neurologic examination (all), test of cognitive function (217)	N , 3; SMR, 3.0 (not significant)	Age, maximal central neural disability score, maximal mental disability score, duration of PTA for model	Only 2% loss to followup Developed model for predicting long-term outcome based on age at injury, worst category of mental and neurophysical disability, length of PT amnesia in selected series

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Reference	Study Design	Population	Type of TBI	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
Teasdale and Engberg, 2001	SMR	145,440 people discharged from hospital with primary or secondary diagnosis of TBI who survived 1 mo after discharge, sampled from Danish National Hospital Registry in 1979–1993, compared with general population	Mild TBI according to following diagnostic categories: concussion (126,114), cranial fracture (7,560), cerebral contusion or traumatic intracranial hemorrhage (11,766)	Suicide as function of diagnosis (concussion, fracture, lesion); from National Cause of Death Registry	Suicide in TBI discharge group compared with Danish population Concussion: SMR, 3.02 (95% CI 2.82–3.25); fracture: SMR, 2.69 (95% CI 2.01–3.59); lesion: SMR, 4.05 (95% CI 3.33–4.93) Women had higher rates of suicide than men in three diagnostic groups; mortality greater in patients injured at age of 21–60 years than in those injured when younger or older	Stratified by age, sex; controlled for substance use	Nationally representative sample Possible underreporting of suicides; accuracy of hospital records No uninjured control group

NOTE: CI = confidence interval, ICD = International Classification of Diseases, MVC = motor-vehicle crash, PTA = posttraumatic amnesia, SMR = standardized mortality ratio, TBI = traumatic brain injury.

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ANXIETY DISORDERS

Anxiety disorders encompass psychiatric conditions that include generalized anxiety disorder (GAD), obsessive–compulsive disorder, panic disorder, acute stress disorder (ASD), PTSD, and social phobias (National Institute of Mental Health, 2008). According to Kessler et al. (2005), about 40 million Americans 18 years old and older, suffer from anxiety disorders, which are often comorbid with alcohol or drug abuse. Several types of anxiety disorders— including PTSD, GAD, and panic disorder—that could be associated with service in the Gulf War have been studied in relation to TBI. They are described briefly below.

PTSD is a psychiatric disorder that can develop after the direct, personal experience of or witnessing of an often life-threatening event. Symptoms that characterize PTSD include re-experiencing of an extremely traumatic event through flashbacks and nightmares, avoidance of things associated with the trauma, and hyperarousal (difficulty in sleeping and in concentrating) (IOM, 2006).

GAD is characterized by chronic anxiety and exaggerated worry. Often, the worries are accompanied by physical symptoms, such as fatigue, headaches, and irritability. Like GAD, panic disorder is accompanied by physical symptoms that may include chest pain, heart palpitations, shortness of breath, dizziness, or abdominal distress due to unexpected and repeated episodes of acute intense fear.

Primary Studies

Bryant and Harvey (1999a) conducted a prospective cohort study to compare rates of ASD and PTSD in motor-vehicle-accident survivors who sustained a mild TBI with rates in survivors without a TBI. Patients were consecutively identified at a major trauma center in New South Wales, Australia, over a 10-month period. Mild TBI was defined on the basis of PTA of less than 24 hours. The study included 79 mild-TBI patients (55 males and 24 females) and 92 patients without TBI (61 males and 31 females) who were evaluated for ASD 2–25 days after trauma. A psychiatric assessment at 6 months after injury included an assessment of ASD through the Acute Stress Disorder Interview and of PTSD through the PTSD module of the Composite International Diagnostic Interview (CIDI). Interviews were completed for 63 (80%) mild-TBI patients and 71 (77%) of the controls. Injury severity score (ISS) was greater in mild-TBI (9.28) than in controls (4.0; $p < 0.001$). During the acute and 6-month followup evaluations, controls reported fear and helplessness more often than patients with mild TBI. They were also more likely to report intrusive memories during the acute phase. There was no significant difference between mild-TBI patients and controls in the rates of ASD—11 patients (14%) and12 patients (13%), respectively—or the rate of PTSD—15 patients (24%) and 18 patients (25%), respectively.

In a separate analysis of the same mild-TBI population, Bryant and Harvey (1999b) evaluated the relationship between PTSD and postconcussive symptoms (PCS). The analysis included were 105 survivors of motor-vehicle accidents who either sustained a mild TBI or did not. At the 6-month followup, 46 mild-TBI patients (32 male and 14 female; mean ISS, 8.96; standard deviation [SD], 6.08) and 59 controls (31 male and 28 female; mean ISS,3.92; SD, 3.74) were evaluated. Assessments administered at 6-months were the PTSD module from the

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CIDI and the Postconcussion Symptom Checklist. Criteria for PTSD were met by nine (20%) of the mild-TBI patients and 15 (25%) of the controls. In analyses comparing patients who had mild TBI and PTSD with those who had mild TBI alone, concentration deficits, dizziness, fatigue, headache, sensitivity to sound, and visual disturbances occurred statistically significantly more often in the mild-TBI patients who had PTSD. Among controls, concentration deficits and irritability were reported statistically significantly more often in PTSD patients than in those without PTSD. In the mild-TBI group, irritability was more common in individuals diagnosed with PTSD than in those who did not.

Creamer et al. (2005) studied 307 individuals who were admitted to a level 1 trauma center to determine the occurrence of PTSD and to assess the relationship between mild TBI, amnesia, and PTSD. Study criteria for mild TBI included LOC of up to 30 minutes, a GCS of 13 or more after 30 minutes, and PTA for up to 24 hours; these criteria were met by 189 (62%) of the subjects. Twelve months after injury, PTSD was diagnosed by trained mental-health clinicians using the Clinician-Administered PTSD Scale for DSM-IV. At 12 months after injury, 10% of the sample met criteria for PTSD: 15% with mild TBI and 7% without TBI ($p = 0.1$).

To the degree that mild TBI is being operationalized as altered mental status or brief LOC marked by "losing time," that raises concern about differential diagnosis of dissociative phenomena, which can characteristically follow an emotional trauma in the absence of a TBI. Dissociation is characterized by a disruption in the integrated functions of consciousness, memory, identity, or perception of the environment. Consequently, ascertainment of mild TBI in contexts in which emotional trauma is likely to co-occur is complicated by potential misclassification of dissociation. That is of particular concern because dissociation at the time of trauma is a known risk factor for PTSD, and the co-occurrence constitutes a potential limitation of both the mild-TBI studies that follow. A recent study by Hoge et al. (2008) examined consequences of mild TBI in US soldiers in two brigades in Iraq that saw a high level of combat during a year-long deployment. About 3–4 months after returning from Iraq, 4,618 soldiers were sent a questionnaire covering injury sustained during combat, combat intensity, physical symptoms, major depression, and PTSD. Mild TBI sustained during combat was determined on the basis of the occurrence of at least one of the following three symptoms: losing consciousness (knocked out), being dazed or confused or "seeing stars," or failure to recall the injury. Of the 2,714 soldiers who returned the questionnaire, 2,525 had complete responses: 124 reported mild TBI and LOC, 260 mild TBI and altered mental status, 435 other injury, and 1,706 no injury. There was a statistically significant association between mild TBI and high combat intensity, a blast mechanism of injury, more than one exposure to an explosion, and hospitalization during deployment. PTSD was present in almost 15% of the soldiers: 43.9% of those with mild TBI and LOC, 27.3% of those with mild TBI and altered mental status, 16.2% of those with other injury and 9.1% of those without injury ($p < 0.001$). After adjustment, PTSD was associated with mild TBI with LOC (OR, 2.98; 95% CI, 1.70–5.24) and with the highest quartile combat intensity compared to the lowest (OR, 11.58; 95% CI, 2.99–44.83).

Schneiderman et al. (2008) conducted a cross-sectional study of military personnel who had served in the conflicts in Iraq or Afghanistan to estimate the occurrence of mild TBI and the prevalence of PTSD and PCS and to examine associations of injury with PTSD and with PCS. The eligible study population included 7,259 veterans of Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) who had left combat theaters by September 30, 2004, and were living in northern Virginia, Maryland, Washington, DC, or eastern West Virginia in

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February 2005. Of those veterans, 2,235 (34%) returned the questionnaire, which included the Brief Traumatic Brain Injury Screen to detect mild TBI and the 17-item PTSD checklist. Twelve percent of the veterans who returned the questionnaire reported a history consistent with mild TBI. Mild TBI was most common among veterans injured by bullets or shrapnel, by blasts, in motor-vehicle crashes, in air or water transport, and in falls. About 11 percent (n, 250) of veterans were classified as having PTSD. Factors associated with PTSD included multiple injuries (prevalence ratio, 3.71 for three or more, 95% CI, 2.23–6.91) and combat mild TBI (prevalence ratio, 2.37, 95% CI, 1.72–3.28). PCS were also associated with PTSD (prevalence ratio, 3.79, 95% CI, 2.57–5.59).

Secondary Studies

The committee identified 10 secondary studies that looked at the association between TBI and anxiety disorders, including PTSD, GAD, and panic disorder. The major limitation of many of these studies was a failure to include a comparison or control group. Other limitations include short followup time and use of small samples.

Three of the secondary studies examined PTSD occurrence after injury but lacked a control group or combined the mild TBI group with other injuries (O'Donnell et al., 2004; Gaylord et al., 2008; Sayer et al., 2008). O'Donnell et al. (2004) reported that 12 months after injury, approximately 20% of patients with mild TBI or other injury met criteria for one or more psychiatric diagnoses; PTSD and major depression were the most common. Similar numbers were reported by Gaylord et al. (2008); 18% of 76 service members had both mild TBI and PTSD. Warden et al. (1997) studied 47 active-duty service members who sustained moderate TBI and neurogenic amnesia for the event and found that none of the patients met the full DSM-III-R criteria for PTSD.

The nature of traumatic memories and their presence or absence may influence whether PTSD develops. Three secondary studies assessed what factors were associated with the development of PTSD after TBI. Gil et al. (2005) assessed the relationship between explicit memory of the traumatic event and the development of PTSD. They observed that respondents who recalled the traumatic event were 4.6 times more likely to have PTSD than those without memory of the event (95% CI, 1.1-9.9).

Two studies report on potential underlying mechanisms of PTSD in TBI. In a brain-imaging study, Koenigs et al. (2007) evaluated which specific areas of the brain were associated with PTSD in Vietnam veterans participating in the Vietnam Head Injury Study. They reported that PTSD was significantly less frequent in veterans who suffered damage to the ventromedial prefrontal cortex (18%) and amygdala (0%) than in those with damage outside these areas (40%) or those with no brain damage (47%). O'Donnell et al. (2007) examined whether tonic and phasic heart rate (HR) as predictive of PTSD in those who suffered trauma (including TBI). The authors observed that phasic HR relative to tonic HR and somatic arousal were the two predictors of subsequent PTSD. That suggests that the extent to which a person's HR increases from resting when recalling the traumatic event is associated with the increased likelihood of PTSD.

Four secondary studies examined anxiety after TBI. Patients with mild TBI were more likely than limb-injured patients to report anxiety in one study (47.4% vs 14.1%; $p < 0.0001$) (Masson et al., 1996). Two other studies observed a similar prevalence of anxiety disorders after

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TBI (Schnyder et al., 2001; Jorge et al., 1993). A recent study by Sayer et al. (2008) of 188 service members who sustained blast or other injuries during OIF or OEF found no difference in the prevalence of anxiety between soldiers exposed to blasts and those exposed to other sources of injury.

Only one study examined the prevalence of panic disorders after TBI (Deb et al., 1999). The authors reported that panic disorder was present in 9% compared with 0.8% of the general population.

Summary and Conclusion

The committee reviewed six primary studies and 10 secondary studies of TBI and PTSD and concluded that the association between a mild TBI and PTSD appears to be different between military and civilian populations. Two of the primary studies and three of the secondary studies were conducted in military populations. The primary studies, which were conducted in military personnel who served in the Gulf War, reported statistically significant associations between TBI and PTSD, but two of the secondary studies found no difference in prevalence with anxiety disorders or PTSD. In contrast, the primary studies conducted in civilian populations did not find an association between TBI and PTSD although an association could not be excluded on the basis of the findings of the secondary studies.

The committee concludes, on the basis of its evaluation, that there is limited/ suggestive evidence of an association between mild TBI and PTSD in Gulf War military populations.

The committee concludes, on the basis of its evaluation, that there is inadequate/insufficient evidence to determine whether an association exists between mild TBI and PTSD in civilian populations.

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TABLE 8.3 Psychologic Outcomes—Anxiety Disorder Studies

Reference	Study Design	Population	Type of TBI	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
Bryant and Harvey, 1999a	Prospective cohort	79 mild TBI (55 males, 24 females), 92 non-TBI patients (61 males, 31 females) 16–65 years old involved in MVAs, consecutively admitted into major trauma hospital for at least 1 day Patients ascertained sequentially over 10-mo period at hospital admission; all assessed at 1 mo; 63 mild TBI (80%), 71 non-TBI (77%) evaluated at 6 mo after trauma Exclusions: drug or narcotic analgesia (except codeine) for first 4 weeks after injury, inability to answer questions, non-English-speaking	Mild, defined as PTA for less than 24 h	PTSD diagnosed with CIDI at 6 mo	ISS greater in mild TBI than in non-TBI group (9.28 vs 4.0; $p < 0.001$) No significant difference in rates of PTSD between groups with mild TBI and no TBI (24%, n , 15; 25%, n , 18, respectively; p value not reported)	None	Head injury ascertained at time arrived at hospital from MVA Good followup over 6-mo period Limitations include lack of control for associated injuries, lack of assessment of duration of LOC on occurrence of PTSD
Bryant and Harvey, 1999b	Prospective cohort	46 TBI (32 male, 14 female), 59 non-TBI (31 male, 28 female) involved in MVAs,	Mild TBI with LOC, PTA <24 h	PTSD module from CIDI and PCS checklist	At 6 mo after trauma, 20% of mild- TBI patients, 25.4%	None	Head injury ascertained at time arrived at hospital from MVA

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Reference	Study Design	Population	Type of TBI	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
Same population as Bryant and Harvey, 1999a		consecutively admitted into major trauma hospital, followed up 6 mo after trauma; 83% of cohort followed to 6 mo Exclusions: drug or narcotic analgesia (except codeine) for first 4 weeks after injury, inability to answer questions, non-English-speaking			of non-TBI patients met criteria for PTSD (p value not reported) No difference between those with and those without PTSD with respect to age, time from trauma to assessment, ISS, length of hospitalization PTSD associated with concentration, dizziness, fatigue, headaches, irritability, visual disturbances (p < 0.01 after Bonferroni adjustment)		Good followup over 6-mo period Overlapping of PCS, PTSD symptoms
Creamer et al., 2005	Prospective cohort	307 patients consecutively admitted into level 1 trauma center with physical injury requiring admission	Mild—included those with LOC ≤30 min, GCS ≥13 after 30 min, PTA ≤24 h	PTSD (determined with CAPS for DSM-IV) associated with PTA (full,	Chronic PTSD diagnosed in 10% of sample (15% in TBI vs 7% in other injury; p, 0.1)	Opioid analgesic administration	Substance-use data not available at time of assessment No control for associated injuries

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Reference	Study Design	Population	Type of TBI	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
		of at least 24 h who experienced mild TBI (189) or no brain injury (118) and were 18–70 years old were followed 1 year after injury Exclusions: injuries due to self-harm, IV drug use, current psychotic disorder		partial, and no recall of event)			Only recall of injury event examined Data on mild TBI and non-TBI controls pooled; relationship between recall and PTSD assessed; therefore, uninformative for mild TBI
Hoge et al., 2008	Cohort	Anonymous survey of 4,618 soldiers, of whom 2,714 (59%) completed questionnaire; of the 2,714, 149 m excluded because of missing data, 40 excluded because they had head injury without LOC Remaining 2,525 US Army soldiers responded 3–4 mo after return from 1 year of Iraqi deployment	Mild 124 (4.9%) LOC 260 (10.3%) altered mental status (such as dazed or confused) 435 (17.2%) other injuries	PTSD	Of 124 (4.9%) with LOC, 43.9% met criteria for PTSD compared with 27.3% of those reporting altered mental status, 16.2% with injuries, 9.1% with no injury Soldiers with mild TBI, LOC more likely to report poor general health, missed workdays, more doctor	95% males, 55.5% under 30 years old, 47.5% junior enlisted rank	After adjustment for PTSD, depression, mild TBI no longer significantly associated with physical health outcomes or symptoms except for headache

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Reference	Study Design	Population	Type of TBI	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
					visits, higher numbers of outcomes or symptoms		
Schneiderman et al., 2008	Cross-sectional	7,259 veterans of OIF, OEF living in northern Virginia, Maryland, Washington, DC, or eastern West Virginia; 2,235 (31%) returned questionnaires	Mild	PTSD, postconcussive symptoms	11% of respondents screened positive for PTSD; factors associated with PTSD included sustained multiple injuries (prevalence ratio, 3.71 for three or more; 95% CI, 2.23–6.19), combat mild TBI (prevalence ratio, 2.37; 95% CI, 1.72–3.28) Postconcussive symptoms strongly associated with PTSD score		Self-reported

NOTE: CAPS = Clinician-Administered PTSD Scale, CIDI = Composite International Diagnostic Interview, ISS = Injury Severity Score, IV = intravenous, LOC = loss of consciousness, MVA = motor-vehicle accident, OEF = Operation Enduring Freedom, OIF = Operation Iraqi Freedom, PCS = postconcussive syndrome, PTA = posttraumatic amnesia, PTSD = posttraumatic stress disorder, TBI = traumatic brain injury.

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OTHER PSYCHIATRIC OUTCOMES

The cost of TBI is enormous from a public-health perspective and likely to be underestimated. There is a high financial cost, determined by a host of acute and chronic injuries in the context of broad and extended personal disability, and the fact that TBI often occurs to soldiers in the course of their duties in war makes this an issue of even greater national concern. The psychiatric aspects of TBI that are most often identified and studied are the related risks of depressive and anxiety disorders, as discussed see above, and well-controlled outcome studies are available from which conclusions regarding associations can be drawn.

TBI has been implicated in other personality and behavioral outcomes, but on the basis of fewer studies, which as likely to have been conducted with less methodological rigor. The other outcomes include aggression, irritability, emotional reactivity, sleep disorders, sexual dysfunction, reduction in insight, and personality disorders, all converging on poor psychosocial function. Complicating the interpretation of the studies is the fact that many studies have been poorly controlled, may have been biased, and may have overlooked pre-morbid factors in the behavioral outcomes. The committee reviewed the literature in this area and found primary studies whose methods were scientific and whose outcomes can be accepted with confidence; these studies are supplemented by secondary studies of suitable rigor that are not definitive.

AGGRESSIVE BEHAVIORS

Primary Studies

Two primary studies found that TBI is associated with subsequent aggressive behavior, but one primary study found no effect of TBI on criminal conviction. A primary study by Ommaya et al. (1996) examined the relationship between aggressive personality traits in TBI. They used military populations and identified “adverse personnel action” and “discharge from military service” as two overall markers of poor outcome in an attempt to understand the relationship between pre-morbid behavior, TBI, and postinjury behavior. The study cohorts consisted of 1,617 active-duty Army personnel who were hospitalized in FY 1992 and FY 1993 for head injuries caused by fighting or for other trauma; the comparison group was all 4,626 active-duty Army personnel who were hospitalized for orthopedic injuries caused by fighting or other means; a “normal” active-duty population of 9,997 (without injury) was a second reference group. The outcomes were “military service discharge” (administrative-behavioral, administrative-criminal, or medical) and other “adverse personnel action”. Several variables were found to be important confounding factors for behavioral discharge and criminal conviction—age, marital status, educational level, pay grade, time in pay grade, and years of active service—and were controlled for in the analyses. Individuals who sustained TBI had a worse behavioral outcome than those who had orthopedic injury, in “adverse action” and “discharge for behavioral criteria or criminal conviction”, whereas TBI did not affect “medical discharge”. Specifically, the percentage of individuals encountering “adverse action” was 21% in the TBI group (overall) and 13% in the orthopedic-injury group (overall); the percentage encountering “discharge for behavioral disturbance or criminal conviction” was 11% and 6%, respectively; and the percentage encountering “medical discharge” was 9% and 11%,

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respectively. When the subpopulation of each group that contracted their injury through fighting was examined, the corresponding percentages for were 34% and 28%, 17%, and 15%, were 1% and 6%, respectively—increased percentages of adverse outcomes in the TBI groups and an attenuation of the TBI effect in each "fighting" subgroup. Overall, TBI increased the risk of behavioral discharge 4 times and of criminal conviction 5 times compared with the normal group; it increased the risk of postinjury adverse action by 1.3 times and decreased the risk of medical discharge by 0.64 times compared with the orthopedic-injury group. "Adverse actions" increased in both the TBI and orthopedic-injury groups 1.75–3 times, but they increased more in the TBI group (3.0 times) than in the orthopedic-injury group (2.1 times). The differences between outcomes in the TBI (fighting) and the orthopedic-injury (fighting) subgroups were not statistically significant. The results of the study suggest that any person sustaining a TBI has a higher risk of later aggressive-behavior problems. Because the outcome measures in the study selected the more severe cases of behavioral impairment, the results may show only the peak of the full problem. Premorbid problems (such as fighting) are a risk factor for postinjury behavioral problems but did not produce worse outcomes in the TBI than in the orthopedic-injury group.

In another primary study, Tateno et al. (2003) assessed aggressive behaviors in 89 TBI cases and 26 multiple-trauma cases (without TBI) consecutively admitted into two Iowa hospitals. Severity of brain injury was measured according to the GCS and PTA and classified with the TCDB. Aggressivity was assessed with the Overt Aggression Scale (OAS) and premorbid aggressive behavior was estimated from premorbid police contact and legal actions. Psychiatric assessments were done by a psychiatrist using the PSE and the Structured Clinical Interview for DSM-IV, along with other standard psychiatric rating scales. Structural neuroimaging scans were also collected. Of the TBI group, 33.7% met the criteria for aggressive behavior in the 6 months after injury (called the aggressive group), compared with 11.5% of the non-TBI injured group; the remaining 66.3% of the TBI group showed low aggressive traits (the nonaggressive group). When the aggressive and non-aggressive TBI subjects were compared major depressive disorder was more frequent in the aggressive group (X^2, 6.54; df, 1; p = 0.01), and the group had a higher Hamilton Depression Rating Score (t, -3.51; df, 87; p = 0.0007) and a higher Hamilton Anxiety Scale scores (t, -3.37; df, 87; p = 0.001). Focal frontal lobe lesions on a magnetic resonance scan occurred more frequently in the aggressive TBI group than in the nonaggressive group (X^2, 8.05; df, 1; p = 0.005), whereas a more diffuse lesion was more frequent in the nonaggressive TBI group.

Virkkunen et al. (1977) examined 1,830 Finnish World Ward II veterans who had received penetrating head injuries and 500 noninjured veteran controls; both groups were followed for up to 37 years. Of the TBI group, 33.1% sustained frontal, 19.5% temporal, 37.7% parietal, and 9.7% occipital lesions. Most veterans in both groups had lifelong employment, despite their injuries. Criminal convictions were no more common in the TBI veterans (5.5%) than in the veteran controls (4.2%), and crimes of violence were not more common in the TBI veterans (0.9%) than in the noninjured veteran group (0.6%). Crimes did not tend to be recurrent in either group.

Secondary Study

Grafman et al. (1996) studied aggression and violence in Vietnam veterans who had TBI and non-brain-injured Vietnam veterans to show that mediofrontal and orbitofrontal lesions of

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the prefrontal cortex are the ones associated with aggression and violence and especially with verbal confrontations. That demonstration of an association between a localized frontal lobe injury and TBI is especially important in light of the considerable literature documenting loss of inhibition and greater aggressive behavior after frontal lobe injury. They hypothesized that lesions to the prefrontal cortex impair the ability to sustain "managerial knowledge" and bias behavior away from plans and social rules toward aggressive and violent behavior.

DRUG AND ALCOHOL ABUSE DISORDERS

Secondary Studies

Many studies have shown a relationship between drug and alcohol use and TBI, and it is generally accepted that drug and alcohol use precedes the TBI and increases the risk of head injury. Therefore, studies have examined post-TBI alcohol use only in the context of previous drug and alcohol use estimated as closely as possible. Horner et al. (2005) focused on the assessment of alcohol abuse and dependence (AA/D) in a 1-year period in a sample of 1,606 TBI patients, randomly sampled from a large state-wide sample of all TBI patients discharged from South Carolina hospitals in 1999–2002 and fully assessed at the time of the incident. A telephone interview a year after TBI was used to obtain information on alcohol use for the month preceding assessment. Overall, 15.4% were heavy drinkers, 14.3%, moderate drinkers, and 70.3% infrequent drinkers or abstainers. Almost all interviewed (99.8%) reported drinking the same or less than a year before; half the current heavy and moderate drinkers were consuming less than they were a year before. Risk factors for heavy drinking were male sex, lower age, substance abuse before TBI, and a diagnosis of depression since TBI.

Jorge et al. (2005) studied 158 Level I TBI patients of whom 24.1% were alcohol-dependent and 10.8% were alcohol abusers; alcohol use during the year before TBI was 34.8%. Of the 55 TBI patients with premorbid AA/D, 30 completed 1 year of followup and 60% of the group followed up resumed their alcohol use; of those 55, 60% developed a mood disorder during the post-TBI year compared with 36.9% of the non-AA/D group. Patients with pre-existing AA/D had reduced cerebral grey matter (GM) volumes compared with patients without AA/D, and post-TBI relapsers had even greater reductions in GM volumes. Moreover, vocational outcome was lower in those with AA/D, especially if it coexisted with mood disorders.

Bombardier et al. (2003) followed a group of consecutively admitted TBI patients over the course of a year. They showed that drinking decreased considerably from before injury to 1 year after TBI: abstinence rates increased from 14% to 36%; people without substantial alcohol-related problems increased from 64% to 84%; and remission of substantial alcohol problems ranged from 30.8% to 56%. However, there was a subset of survivors (about 25%) who drank heavily at 1 year after TBI, and the level of pre-TBI alcohol use predicted who would be in the post-TBI heavy-drinking group. That suggests that drug and alcohol use should still be monitored after TBI.

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PSYCHOTIC DISORDERS

Primary Studies

Fann et al. (2004) used the Group Health Cooperative (GHC) of Puget Sound (450,000 members) in a prospective cohort study of TBI. All GHC members with a new diagnosis of TBI in 1993 who had been GHC members for at least a year were examined, evaluated for severity and matched with randomly selected GHC non-TBI members by sex, age, and enrollment date. Psychiatric illness was assessed for the year preceding TBI and for the 3-year period after TBI, as noted by the presence of a psychiatric diagnosis, filling of a prescription for a psychiatric medication, or use of psychiatric services. Psychiatric diagnoses were made according to ICD-9-CM by primary-care physicians. The authors collected 939 cases of TBI in 1993, for an overall annual TBI incidence of 475.2 per 100,000 person-years; 85.5% of the TBIs were mild. The risk of psychiatric illness was significantly increased after mild and moderate-severe TBI. Increased ORs were observed especially in patients with no prior history of psychiatric illness, within the first year after TBI: the OR was 2.1 (95% CI, 1.6–2.6) in those with mild TBI and 3.4 (95% CI, 1.9–5.8) in those with moderate to severe TBI. An approximate 1.5-fold increase in risk of psychiatric illness was also observed in the following 3 years in patients who had a diagnosis of a psychiatric illness before sustaining a mild TBI; no association was observed in such patients who sustained a moderate to severe TBI. Specifically, the new onset of a psychotic disorder were no greater after mild TBI in the following 3 years than in the year before the TBI, whereas after moderate to severe TBI, a diagnosis of psychosis were greater but not until the second and third years: 1–12 months after TBI, the OR was 2.8 (not significant); 13–24 months after TBI the OR was 5.9 (95% CI, 1.6–22.1); and 25–36 months after TBI the OR was 3.6 (95% CI, 1.0–12.3). The OR for any psychiatric diagnosis during the 3-year followup was increased considerably if there was a prior psychiatric illness.

Secondary Studies

A study by Achte et al. (1969) also found an association between TBI and psychosis. Data were collected in a Finnish hospital for brain injuries that housed all central nervous system–injured war veterans of the 1939–1945 Finnish Wars; 3,552 men comprise this cohort followed for 22–26 years. About 42% had a penetrating head wounds (shell splinters and gun shot wounds), and 58% had closed TBI. In this population, 317 (8.9%) out of the 3,552 veterans had had a diagnosis of psychosis (a rate that is 2–3 times the usual population-based rate of approximately 3–4%). In addition, 30.4% had epilepsy (44.2% of those with penetrating head injuries and 20.3% of those with closed TBIs), and 8.9% had aphasias (16.1% of those with penetrating head injuries and 3.7% of those with closed TBIs).

Godfrey et al. (1993), in a small but well-controlled study focusing on insight, found poor insight regarding behavioral impairment at 6 months after TBI. The defect appeared to attenuate with time. Increased insight regarding behavioral impairment was accompanied by emotional dysfunction. Henry et al. (2006) compared a group of TBI patients with their friends and close relative for their ability to identify their own emotions (an aspect of insight) and found the TBI group impaired, less able to recognize emotion in others, externally oriented and less fluent on tests of semantic fluency.

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Summary and Conclusions

Aggressive Behaviors

The committee concludes, on the basis of its evaluation, that there is sufficient evidence of an association between TBI and subsequent development of aggressive behaviors. Additional evidence that aggression is associated with TBI primarily when frontal cortical lesions are sustained is consistent with a large literature associating frontal lobe damage with loss of behavioral control.

Alcohol and Drug Abuse

The committee concludes, on the basis of its evaluation, that there is limited/suggestive evidence of an association between TBI and decreased drug and alcohol use, as compared with preinjury levels, in the 1 to 3 year period following the TBI.

Psychosis

The committee concludes, on the basis of its evaluation, that there is limited/suggestive evidence of an association between moderate or severe TBI and psychosis. However, even if the TBI is severe, the psychosis does not appear during the first post-TBI year, but rather, becomes apparent in the second and third post-TBI years.

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TABLE 8.4 Psychologic Outcomes—Personality Disorder Studies

Reference	Study Design	Population	Type of TBI	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
Fann et al., 2004	Prospective cohort	939 HMO enrollees (479 women, 460 men) with diagnosed TBI in 1993 enrolled in health plan for at least 1 year before injury, 3 to 1 match with health plan controls; followed up to 3 years after enrollment in study	Mild (803), moderate to severe (136); injury identified with ICD-9-CM categories, codes (fracture of vault base of skull; other, unqualified, multiple fractures of skull; intracranial injury)	Psychiatric illness determined with three major indicators: ICD-9-CM codes, prescriptions, psychiatric-service use in year before TBI, 1–12 mo, 13–24 mo, 25–36 mo after injury	Increased rates of psychiatric illness in year after TBI (49% in moderate to severe, 34% in mild, 18% in non-TBI comparisons) TBI associated with higher risk of adjustment reaction in year after TBI: mild, 7.2%; moderate to severe, 7.4%; controls, 4.6% TBI associated with higher risk of psychotic disorder in year after TBI: mild, 3.0%; moderate to severe, 13.0%; controls, 1.9%	Age, sex, TBI reference date, logarithm of costs in year before TBI reference date, comorbid injuries	Possible misclassification of diagnoses; lack of precision in measurement of TBI exposure Control group is general HMO population, not injury population Had preinjury data
Ommaya et al., 1996	Retrospective cohort	2,243 TBI military hospital patients from discharge records for all military hospitals vs	TBI severity determined with ICD-9 to compute AIS and ISS; mild	Post-TBI discharge from active-duty service for: behavioral reasons, criminal	Behavioral: mild TBI, OR, 1.8 (95% CI, 1.4–2.2); moderate TBI,	Stratified by whether injuries arose from fights	Alcohol use not considered Normal orthopedic controls

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Reference	Study Design	Population	Type of TBI	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
		active-duty population (1,879,724), followed up 2.7 years after injury	(1,778), moderate (174), severe (274)	conviction, alcohol and drug abuse, medical disability, death	NS; severe TBI, NS Alcohol, drug abuse: mild TBI, OR, 2.6 (95% CI, 1.6–4.3); moderate TBI, OR, 5.4 (95% CI, 1.7–16.9); severe TBI, NS Criminal conviction: mild TBI, OR 2.7 (95% CI, 1.9–3.9); moderate TBI, NS; severe TBI, NS		
Tateno et al., 2003	Retrospective cohort	89 patients with closed head injury admitted into University of Iowa hospitals and clinics, Iowa Methodist Medical Center; 26 patients with multiple traumas but without brain damage or spinal-cord injury	TBI severity determined with GCS, Traumatic Coma Data Bank; mild (50), moderate (19), severe (19), 1 missing	Aggressive behavior assessed with Overt Aggression Scale; mood, anxiety disorders assessed by psychiatrist	30 (33.7%) TBI patients presented with aggressive behavior during first 6 mo compared with three (11.5%) controls ($p < 0.03$)		

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Reference	Study Design	Population	Type of TBI	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
Virkkunen et al., 1977	Retrospective cohort	1,830 Finnish veterans of WWII with penetrating brain injuries, 500 noninjured Finnish WWII veterans as controls		Criminal convictions in Finland collected from Criminal Register	100 (5.5%) TBI patients, 21 (4.2%) controls convicted of crimes (NS)		

NOTE: AIS = Abbreviated Injury Scale, CI = confidence interval, GCS = Glasgow Coma Scale, HMO = health-maintenance organization, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, ISS = Injury Severity Score, NS = not significant, OR = odds ratio, TBI = traumatic brain injury, WWII = World War II.

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SOCIAL FUNCTIONING

Traumatic brain injury (TBI) can lead to disruptions in higher-level functions of everyday life, including social relationships, independent living, employment, and leisure activities. Social functioning is evaluated by using global outcome scales, such as the Glasgow Outcome Scale (GOS) (Jennett and Bond, 1975) and the GOS-Extended (Wilson et al., 1998); rates of return to work and independent living; or questionnaires that typically include self-reported measures of health-related changes in functioning in everyday life, such as the Sickness Impact Profile (SIP) (Bergner et al., 1976). This chapter first discusses primary studies of military and civilian populations and then secondary studies grouped by outcome, including both military and civilian populations because their findings are generally similar.

PRIMARY STUDIES OF MILITARY POPULATIONS

Penetrating Head Injury

Schwab et al. (1993) evaluated work status in a group of 520 Vietnam War veterans who sustained penetrating head injury in 1967–1970 and were seen for a 15-year followup. Subjects were drawn from the W.F. Caveness Vietnam Head Injury Study registry (see Chapter 5) and compared with 85 controls recruited from the Veterans' Administration files of uninjured soldiers who had served in Vietnam during the same years and were in the same age range as the TBI subjects. Of the injured veterans, 56% were working at the 15-year followup, compared with 82% of the uninjured controls ($p < 0.0001$). Work status was strongly and linearly associated with the number of residual disabilities, including posttraumatic epilepsy, paresis, visual-field loss, verbal-memory and reasoning loss, visual-memory loss, psychologic problems, and self-reported violent behavior. Brain-volume loss and post injury evaluation of intelligence based on the Armed Forces Qualification Test explained similar amounts of variance in work status, as did the number of residual disabilities (Schwab et al., 1993).

Closed Head Injury

Ommaya et al. (1996) determined that discharged military personnel who had sustained TBI were more likely to be discharged because of behavior than the total discharge population. They identified 2,226 military personnel who sustained a TBI in 1992 through hospital-discharge records of all military hospitals. Information about discharge from military service was obtained for 2.7 years after injury and compared with the total discharge population of 1,879,724.

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Discharge from military service because of behavior (for example, problems with motivation, misconduct, discreditable occurrences, or a series of minor discipline problems), criminal conviction, alcohol or drug abuse, or medical disability were examined by TBI severity as classified with the Abbreviated Injury Scale (AIS) head score. Compared with the total discharge population, discharge due to alcohol or drug abuse was more frequent in those with moderate TBI (odds ratio [OR], 5.4; 95% confidence interval [CI], 1.7–16.9) and those with mild TBI (OR, 2.6; 95% CI, 1.6–4.3) but not in those with severe TBI. Discharge due to behavior was no different in those with moderate or severe TBI and 1.8 times greater in those with mild TBI (95% CI, 1.4–2.2). Discharge due to criminal conviction was 2.7 times higher in those with mild TBI (95% CI, 1.9–3.9) and no different in those with moderate or severe TBI. Discharge due to medical disability was 7.5 times higher in those with mild TBI (95% CI, 6.0–9.3), 25.2 times higher in those with moderate TBI (95% CI, 16.2–39.2), and 40.4 times higher in those with severe TBI (95% CI, 30.0–54.4). The authors note, however, that because the risk of medical discharge is directly related to the severity of the injury, these individuals may be receiving medical discharges rather than other types of discharges (such as behavioral). A limitation of the study is that it did not take into account pre-existing factors, such as aggressive tendencies or preinjury alcohol abuse, which may have played a role in discharge outcome.

In a related study, Ommaya (1996) examined 1,617 patients admitted to hospitals for TBI in 1992 and 1993, 4,626 patients admitted for orthopedic or internal injuries, and a random sample of 9,997 active-duty Army subjects to compare rates of discharge from military service based on behavioral criteria. After adjustment for confounders (age, sex, marital status, educational level, pay grade, months in current grade, years of active-duty service, injury severity, and preinjury "adverse action", disciplinary action recorded in a soldier's personnel file), head injury was related to an increased risk of behavioral separation (relative rate [RR], 4.01; 95% CI, 3.54–4.94) and criminal conviction (RR, 4.99; 95% CI, 3.62–6.87) compared with the random sample of active-duty Army personnel. Head injury also was related to an increased risk of post injury adverse action (RR, 1.31; 95% CI, 1.14–1.51). In addition, the risk of medical discharge was lower in the head-injured group than in the orthopedic- or internal-injury group (RR, 0.64; 95% CI, 0.51–0.80).

McLeod et al. (2004) examined employment retention in the British Army in a group of 564 British Army personnel who had sustained a TBI in 1994, a group of 368 British Army personnel who had a lower-limb fracture in 1994 (and did not sustain any other injuries), and a group of 25,575 healthy army personnel. All those with TBI were admitted to the hospital or medical center and were selected if they had International Classification of Diseases (ICD) codes indicating TBI and did not have other ICD injury codes. Employment retention in the Army was examined with Kaplan-Meier survival analysis, stratifying for age (16–24, 25–28, 29–33, and >34 years), which roughly paralleled career steps in the Army. The results indicated that in the youngest group (16–24 years old), healthy subjects left the Army earlier than subjects in either injury group: in a median of 1.74 years, compared with 3.91 years for those with TBI and 4.39 years for those with lower-limb fractures. An opposite pattern was observed in the oldest group (34 years old and older): healthy subjects served the longest: a median of 5.55 years, compared with 3.33 years for those with TBI and 3.75 years for those with lower-limb fractures. Subjects 34 years old or older had the lowest employment retention: 69% of them in the TBI group continued in the Army beyond year 1, and 19% were still employed at year 6, compared with 85% of the fracture group employed at year 1 and 26% at year 6 and 80% of the healthy group at year 1 and 48% at year 6 ($p < 0.001$). The authors discuss the possibility that the greater drop in

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employment in the TBI group 34 years old or older reflects the likelihood that older people are typically in positions of greater responsibility in the Army, including leadership and managerial positions. They theorize that the TBI group may have had a disproportionate amount of difficulty in maintaining employment after injury, which led to an increase in medical discharges.

PRIMARY STUDIES OF CIVILIAN POPULATIONS

Dikmen et al. (1995) examined 466 people with TBI and compared them with 124 trauma controls (people who had sustained bodily injury but not to the head) and with 88 healthy friend controls (people who had not sustained any injury). Subjects were drawn from three prospective longitudinal studies of outcome and were followed from the time of injury until a year after the injury (see Chapter 5). Social functioning was evaluated with the GOS, a rating based on dependence on others for self-care and the ability to participate in normal social life. A structured interview provided information about independent living, school, employment, and income. The SIP, a self-report measure of functioning in 12 activities of living, was also administered. The subjects with TBI were stratified by severity of injury. More severe TBI was related to worse outcome compared to trauma controls on all measures of social functioning except return to school. The absence of a detectable difference in rates of return to school between TBI and trauma controls might reflect the requirement that schools accommodate students with a variety of disabilities. A higher proportion of patients in each of the TBI severity groups except the most mildly injured, was rated as significantly disabled, according to the GOS, than the trauma controls—for example, percentage with good outcome: trauma controls, 93%; With respect to the TBI group, those with time to follow commands (TFC) 1–6 days, 69%; TFC 7–13 days, 59%; TFC 14–28 days, 31%; TFC over 28 days, 10%; Glasgow Coma Scale (GCS) 9–12, 64%; GCS 6–8, 38%; GCS 3–5, 26% ($p < 0.05$ by Tukey's post hoc comparison for each TBI severity group indicated vs trauma controls). Statistically significantly fewer TBI subjects (76%) than trauma controls (93%) returned to living independently at 1 year after injury ($p < 0.001$). Increasing length of coma was significantly related to decreasing likelihood of returning to independent living at 1 year: those with less than 1 hour of coma, 89%; 1–24 hours, 89%; 1–6 days, 74%; 7–13 days, 49%; 14–28 days, 55%; and 29 days or longer, 23% ($r = 0.49$; $p < 0.001$). Fewer TBI subjects (49%) than trauma controls (63%) were working 1 year after injury ($p < 0.05$). The more severe the TBI, the less likely the person returned to work: of those with less than 1 hour of coma, 64% had returned to work; 1–24 hours, 50%; 1–6 days, 51%; 7–13 days, 36%; 14–28 days, 18%; and 29 days or longer, 6%. In a subgroup of the same sample, McLean et al. (1993) also found a lower rate of return to work in participants with TBI than in friend controls ($p < 0.01$). The TBI subjects earned less than trauma controls in the year after injury, and within the TBI group increasing length of coma was associated with decreasing income (Dikmen et al., 1995).

TBI subjects reported more dysfunction than trauma controls on the SIP, especially on scales assessing psychosocial, rather than physical, limitations. For example, the TBI subjects (mean, 23) reported significantly more dysfunction than the trauma controls (mean, 14) on the Work Scale ($p < 0.001$) and on the Psychosocial Summary Scale (mean dysfunction, 11 vs 8, respectively; $p < 0.01$), indicating difficulties in communication, alertness behavior, emotional behavior, and social interaction. There were no significant differences between TBI patients and trauma controls on the Physical Summary Scale, which evaluates ambulation, mobility, body

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care, and movement. The SIP total mean score for trauma controls showed significantly less difficulty than in TBI subjects with coma length of 1 week or more: trauma controls, total mean score, 6; TBI patients with coma length of 7–13 days, SIP mean, 12 ($p < 0.05$); 14–28 days, 14 ($p < 0.01$); 29 days or more, 17 ($p < 0.001$). There was a significant relationship between TBI severity and reported dysfunction on the SIP on all scales except emotional behavior ($p < 0.01$) (Dikmen et al., 1995).

In a separate analysis of a subgroup of the same population, Dikmen et al. (1994) examined time to return to work in 366 TBI patients and 95 trauma controls who worked before their injury (see Chapter 5). Preinjury workers were followed for 1–2 years after injury to measure the time from injury until the first return to work regardless of the length of that employment. Time to return to work was significantly and systematically related to TBI severity. For the measure of TFC, a measure of coma length, patients with TBI who had milder injuries went back to work more often and earlier than those with more severe injuries: 87% of trauma controls had returned to work by 1 year after injury, 82% returned with TFC of up to 5 hours, 67% with TFC of 6–24 hours, 67% with TFC of 1–6 days, 46% with TFC of 7–13 days, 21% with TFC of 14–28 days, and 6% with TFC of 29 days or longer ($p < 0.0001$). Similar relationships were found with other TBI-severity indexes, such as the GCS, and with neuropsychologic functioning at 1 month after injury, the latter representing the combined effects of injury severity and pre-morbid functioning.

Doctor et al. (2005) conducted a prospective cohort study to examine the same population as Dikmen et al. (1994) and additional TBI subjects from another prospective investigation. Work rates were examined at 1 year after injury in 418 TBI subjects who were working before their injury and compared with expected unemployment rates from the current population survey (United States Department of Labor, 2002). There was a substantial increase in the risk of unemployment of patients with TBI that increased with severity: 31% of TBI patients with a GCS of 13–15 were unemployed compared with the expected unemployment rate of 8.8% (RR, 3.46; 95% CI, 2.87–4.28), 46.4% of TBI patients with a GCS of 9–12 were unemployed compared with the expected unemployment rate of 9.6% (RR, 4.85; 95% CI, 3.71–6.02), and 62.1% of TBI patients with a GCS of 3–8 were unemployed compared with the expected unemployment rate of 10.4% (RR, 5.98; 95% CI, 4.92–6.96).

Edna and Cappelen (1987) followed for 3–5 years after injury a prospective Norwegian cohort of 485 people who sustained closed head injuries in 1979 and 1980 and 89 controls who were admitted to the hospital over the same period with acute appendicitis. Subjects were followed to examine work status and social condition as evaluated with a questionnaire. The majority of the head-injured subjects had mild injuries; 89% had a GCS of 13–15. Unemployment in the head-injured increased from 12% before injury to 27% after injury; unemployment in the controls increased from 5% to 16% ($p < 0.01$). However, unemployment increased substantially more in head-injured subjects who were 45 years old or older (from 16% to 53%) compared with head-injured subjects who were less than 45 years old (from 11% to 20%). Social outcome was slightly less favorable in the subjects with closed head injuries than in the controls with respect to contact with friends, family life, and income.

Oddy et al. (1978) examined 54 people who had closed head injuries and 35 controls with traumatic limb fractures and no head injury, matched on age and socioeconomic status. The head-injured were a consecutive series of patients who had had posttraumatic amnesia (PTA) of more than 24 hours and were followed until 6 months after injury. Work outcome and social

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outcome were evaluated with a semistructured interview, the Katz Adjustment Scale (Katz and Lyerly, 1963), a task-distribution checklist, the Wakefield Depression Inventory (Snaith et al., 1971), and a scale for activities of daily living. Close relatives of the head-injured were also interviewed as a secondary source of information. Return to work by 6 months after head injury was significantly associated with injury severity. A higher percentage of TBI participants who had less severe injuries than of those with longer periods of PTA were back at work by 6 months after injury. The percentage of participants who had returned to work by 6 months decreased with increasing length of PTA: 97% of the control group, 81% of the head-injured participants with PTA of 1–7 days, and 50% of those with PTA of over 7 days ($r = 0.41$; $p < 0.003$). Leisure activities were impaired in 33% of the head-injured subjects with PTA of 1–7 days (not significant) and 42% of those with PTA of over 7 days ($p < 0.01$). However, the control group also reported a significant reduction in leisure activities ($p < 0.01$), so disruption might not have been specific to brain injury. Social interaction was assessed by number of close friends and acquaintances, frequency of visits, social outings, social discomfort, and loneliness. There was no evidence of disruption in social interaction in the head-injured group as a whole, but the most severely injured group (PTA of over 7 days) experienced a significant decrease in number of friends ($p < 0.04$) and were more dependent on parents than before injury ($p < 0.02$).

Gerberich et al. (1997) examined academic performance before and after TBI in university undergraduate students. Cases were 99 undergraduate students who sustained a brain injury requiring hospitalization during 1980–1984, and there were two comparison groups: 198 uninjured controls with no documented injury that necessitated hospitalization and 121 injured controls who were hospitalized for an injury other than brain injury during the same period. Most (90%) of the brain-injured subjects sustained mild injuries according to the GCS. All participants were followed from the time of university admission through the end of the winter quarter of 1985; this allowed a minimum of 3 quarters of school after entry into the study. No significant differences in academic performance were found between groups. However, female participants with a brain injury had a significant pre- to post-injury decrease in grade-point average compared with both uninjured and injured controls (each $p < 0.02$). This finding was not observed in male participants.

Bond and Godfrey (1997) compared videotaped social interaction sessions in 62 patients with TBI who had PTA exceeding 24 hours and were between 6 months and 3 years post-injury to 25 orthopedic controls from the same hospital. Patients with a history of neurologic, psychiatric, or alcohol-related discords, as well as those with prior moderate to severe TBI were excluded. Both groups were studied via their participation in videotaped social interactions sessions, which were observed and rated by four undergraduate psychology students for impressions and micro-behaviors, including appropriateness, and for deferral, interest, prompt frequency, and turn duration. TBI and control subjects were videotaped in an unstructured 15-minute conversation with female assistant blinded to group status. Impression ratings were made by four raters, blinded to group status, with 12 hours training (rating test subjects and comparing against established ratings until 95% agreement within 2 points between the 4 raters). They rated conversations as “appropriate,” “effortful,” “interesting,” and “rewarding” on a 9-point Likert scales. Micro-behaviors were examined by one rater, blinded to group status, with training until 90% agreement with another rater, rated turn duration and prompt frequency for both subject and assistant (4 measures). A second rater rated 25% random sample, with interclass correlation 0.92-0.99. The TBI subjects’ conversations were rated as significantly less interesting, less appropriate, less rewarding, and more effortful than those of control subjects. They were also

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characterized by differences in the frequency of prompt usage and turn duration. The authors concluded that TBI subjects are beset by problems in their social communication and behavior.

Friedland and Dawson (2001) followed 99 people who were in a motor-vehicle accident (MVA); 64 sustained a mild TBI, and 35 did not. The participants were recruited from consecutive admissions over a 20-month period ending in April 1994. Mild TBI was defined as an initial GCS score of at least 13 (after 30 minutes), loss of consciousness (LOC) of no more than 30 minutes, or PTA of no more than 24 hours. Subjects who did not have a mild TBI all had a GCS of 15, no documented LOC or PTA, normal computed tomography (CT) findings (if CT was done), and no documentation regarding brain injury in the medical chart. Both groups had high mean injury-severity scores (ISS) (mild TBI, 21.09; no mild TBI, 18.17). At 6–9 months after injury, participants were assessed with the Reintegration to Normal Living (RNL) Scale, with the SIP, and according to return to work. Posttraumatic stress disorder (PTSD) was also evaluated with the Impact of Event Scale and the General Health Questionnaire. The mild-TBI group reported significantly more dysfunction on the psychosocial summary score of the SIP than those without mild TBI ($p = 0.01$). There were no other significant differences between the groups on the SIP, nor were there any significant differences between the groups on the RNL Scale or in return to work (44% of the mild-TBI and 41% of the group without mild TBI had returned to work at the time of outcome assessment). The group with mild TBI had a higher risk of PTSD (OR, 1.043; 95% CI, 1.001–1.067).

Stulemeijer (2006) assessed 299 mild-TBI subjects admitted to an emergency department (ED) level 1 trauma center in the Netherlands 6 months after injury. They divided the group into the 89 who sustained additional injuries to the body and the 210 who sustained only mild TBI and compared them with 261 control subjects who attended the ED after suffering wrist or ankle distortions 6 months earlier. Mild TBI was defined as an impact to the head with or without LOC of up to 30 minutes, with or without PTA, and a hospital admission GCS of 13–15.

Although all had GCS scores in the range of 13 to 15, subjects with mild TBI and additional injuries suffered significantly more severe TBI using other indices, than those with only TBI, for example, mean Abbreviated Injury Scale (AIS) head score in mild TBI with additional injuries was 2.3 compared with a mean score in isolated mild TBI of 1.9 ($p = 0.0001$). At 6 months after injury, social functioning was assessed with the SF-36 Physical Functioning and Social Functioning scales, the SF-36 Perceived Health change, and change in work, defined as a loss of work or change in work status—working fewer hours or working in a lower-level occupation because of the injury. Analyses were adjusted for age, sex, and AIS head score. Each SF-36 measure differed significantly between the groups (each $p = 0.0001$). The subjects with mild TBI and additional injuries showed more dysfunction than the mild-TBI-only subjects, and both showed more than the minor-injury controls (each $p < 0.001$). Change in work status also differed significantly between the groups ($p = 0.0001$): 35% of the subjects with mild TBI and additional injuries, 14% of the mild-TBI-only subjects, and 2% of the controls reported change in work status at 6 months after injury. The location and severity (defined as ISS over 15) of the additional injuries were each significantly related to the SF-36 Physical Functioning scale (each $p < 0.01$), and subjects with multiple injuries or injuries to the extremities or the chest or abdomen reported more problems. There were no differences by severity and location on the other scales.

Heitger et al. (2007) examined 37 persons with mild closed head injury and 37 normal controls matched to the head-injured on age, sex, and years of education. The mild closed head

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injured subjects all had their first assessed GCS equal to 13–15, and none decreased to below 13 while they were in the hospital, and all had PTA of less than 24 hours. Social functioning was assessed with the Rivermead Head-Injury Follow-up Questionnaire (RHIFQ) and the SF-36 at 6 and 12 months after injury. The results showed no significant differences between the mild closed head injured subjects and controls on the SF-36 at 6 and 12 months after TBI. The RHIFQ was not used in controls, because it measures perceived change in ability as the result of injury. At 6 months after injury, 27% of the mild close head injured subjects reported mild change or worse in perceived ability in one or more activities; this decreased to 23% at 12 months after injury. Finding that work was more tiring was the most common complaint at both times, reported as at least a mild problem by 14% at 6 months and 23% at 12 months. Other activities reported as presenting at least a mild problem by 10% or more of the subjects were maintaining previous workload at both 6 and 12 months and coping with family demands and having a conversation with two or more people at 12 months. In contrast, 49% and 61% at 6 and 12 months, respectively, reported no changes in any activity after injury. It is not possible to determine whether the results of the study are related to the TBI or to other injuries.

SECONDARY STUDIES

Results of many secondary studies support what has been found in primary studies. Their most common limitation is lack of a control group or small samples. Secondary studies have examined effects of TBI on major activities (work or school), independent living, social relationships, leisure activities, functional status, and quality of life and effects on the primary caregivers of people who have TBI.

Major Activities (Work or School)

Many secondary studies have reported an association between TBI and low rate of return to work, especially in those with moderate or severe TBI (Dikmen et al., 1993; Kersel et al., 2001; Mazaux et al., 1997; van Zomeren and van Den Burg, 1985; Walker and Erculei, 1969). For example, Dikmen et al. (1993) studied a group of 31 moderately to severely injured adults and compared them with 102 friend controls. They reported that 33% of the preinjury workers were able to return to work at 1 year and 46% at 2 years after injury, whereas 85% of the friend controls were working at 1 year. Kersel et al. (2001) examined a New Zealand sample of 65 people 6 months and 1 year after they sustained a severe TBI. In their sample, 13% of the preinjury workers were back to work at 6 months and a further 20% at 1 year, 38% of the preinjury students had returned to school at 6 months and 54% at 1 year. Van Zomeren and van Den Burg (1985) assessed 57 people with severe TBI 2 years after injury; 58% reported that they had resumed their former work or study without any changes, 13% had resumed their former work but with lower demands (for example, working part-time), 5% had not resumed their former work but were working at a lower level, 7% were working in a socially sheltered environment, and 16% were not working at all. Mazaux et al. (1997) reported that 58% of preinjury workers had returned to work and 74% of preinjury students had returned to school at 5 years after injury in their sample of subjects who had mild to severe TBI. Walker and Erculei (1969) followed a group of 343 World War II veterans 14–17 years after they sustained a TBI; 39% were not working or were working only irregularly.

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There appears to be a strong relationship between rate of return to work and the severity of TBI. Whiteneck et al. (2004) conducted a population-based study of persons hospitalized for TBI in Colorado. They followed 1,591 adult TBI patients to 1 year after injury and found that the severity of the injury made a significant difference ($p < 0.01$) in rate of return of preinjury workers: 47% of those with severe injuries (defined as a GCS of up to 8) had returned to work, 78% with moderate injuries (GCS, 9–12), and 80% of those with mild injuries (GCS, 13–15). Dikmen et al. (2003) followed 210 people with complicated mild to severe TBI up to 3–5 years after injury. Rate of return to work varied significantly with TBI severity ($p < 0.05$) as measured with a modified AIS head score: 73% of preinjury workers with a score of 3 were back to work, 66% with a score of 4, and 49% with a score of 5. The lowest rate of return to work occurred in the group with an AIS head score of 5 and both an anatomic lesion and a TFC greater than 24 hours: only 29% of this group had returned to work 3–5 years after injury. Engberg and Teasdale (2004) used a national hospital register to select subjects who had sustained a TBI in 1982, 1987, or 1992 with ICD codes that indicated either a cranial fracture or a cerebral lesion. The followup period was 5, 10, or 15 years after injury. They reported differences in the rate of inability to work between the cranial-fracture group and the more severely injured cerebral-lesion group at each followup period. No one in the cranial-fracture group reported being unable to work at the 10- and 15-year followups, and only 14% said that they were unable to work at the 5-year followup. In the cerebral-lesion group, 23% at the 15-year followup, 29% at the 10-year followup, and 31% at the 5-year followup said that they were unable to work. The authors cautioned that although it is not clear that these findings are due entirely to the TBI, the differences between the two groups suggest that severity of brain injury is a factor.

Return to work has also been associated with computed-tomography (CT) findings. Grosswasser et al. (2002) examined CT findings on TBI subjects and compared them with vocational outcome in a group of Vietnam War veterans participating in the Vietnam Head Injury Study. A group of 74 subjects with penetrating head injury and 37 with closed head injury were evaluated 12–14 years after injury. The results indicated that total brain-volume loss, third ventricle width, ventricular score, and septum–caudate distance were significantly related (each $p < 0.01$) to return to work in the cases with penetrating head injury.

There is some evidence that work stability after TBI is related to the severity of the injury. Machamer et al. (2005) examined stability of work up to 3–5 years after injury in a group of 165 preinjury workers who had sustained complicated mild to severe TBIs. Severity of injury and associated impairments were related to amount of time worked after injury. Once a worker returned to work, the ability to maintain uninterrupted employment was related to premorbid characteristics, such as being older or having a higher income.

Some studies using different groups of subjects compared characteristics of persons with TBI who are employed at followup with those who are not employed (Drake et al., 2000; Cifu et al., 1997; Fraser et al., 1988; Walker and Erculei, 1969). In general, the results of those studies have indicated that subjects who are employed at followup had less severe injuries and do significantly better on neuropsychologic and functional-status measures administered acutely or concurrently than persons with TBI who are not employed at followup. For example, Cifu et al. (1997) compared the employed and unemployed at 1 year after injury in a group of 132 TBI subjects who were participants in the Traumatic Brain Injury Model Systems project. The severity of the injury was significantly different between the groups: the employed group had significantly milder initial GCS scores, shorter comas, and shorter periods of PTA (each p <

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0.05) than the unemployed group. Functional status was assessed with the Functional Independence Measure (FIM) (Forer, 1987) and the Disability Rating Scale (DRS) (Rappaport et al., 1982) at rehabilitation admission and discharge. Unemployed persons were functioning at a significantly lower level than the employed at rehabilitation admission on the FIM ($p < 0.01$) and the DRS ($p < 0.001$) and at rehabilitation discharge on the DRS ($p < 0.01$). The unemployed group also scored significantly lower than the employed on a memory-delay test ($p < 0.05$). Fraser et al. (1988) found poorer neuropsychologic test scores at 1 month and 1 year after injury and more dysfunction on the SIP physical scales at 1 month after injury in those who failed to return to work by 1 year after injury than in those who had returned.

Studies of vocational outcome after mild TBI have had mixed results: some have found good rates of return to work or at least rates no different from those in a control group (Dikmen et al., 1986; Boake et al., 2005), and others have suggested that mild TBI has a lingering effect (Vanderploeg et al., 2007, 2003). Dikmen et al. (1986) studied a group of 19 persons with mild TBI. At 1 year after injury, 15 (79%) had returned to their major role activities (such as work, school, or homemaking) without limitations. Boake et al. (2005) examined time to return to work in 210 people with mild or moderate TBI and 122 trauma controls. All the TBI subjects had closed head injuries, and 90% had mild injuries. The rate of return to work was similar in TBI subjects (61%) and trauma controls (62%) 6 months after injury. Most of the mild-TBI subjects and nonhospitalized trauma controls were back to work by 3 months after injury, but most of the moderate-TBI subjects had not returned to work at 6 months after injury.

In contrast, Vanderploeg et al. (2003, 2007) conducted a series of studies of the role of self-reported mild TBI not requiring hospitalization in long-term outcome and factors that could predict outcome. They used the Vietnam Experience Study cohort of Army veterans about 16 years after military discharge and collected information on health-related events that may have occurred from military discharge to the time of the study. A sample of veterans was categorized into three groups according to their responses on a questionnaire: 3,214 veterans with no MVA and no TBI (normal controls), 539 veterans who were injured in an MVA but had no TBI (MVA controls), and 254 veterans who had self-reported TBI with altered consciousness but no hospitalization (mild TBI). ORs were adjusted to control for differences between the groups on demographics, prior or current medical conditions, and preinjury psychiatric conditions. The mild TBI group had increased odds of being employed less than full-time (adjusted OR, 1.89; 95% CI, 1.36–2.64), an annual income less than $10,000 (adjusted OR, 1.88; 95% CI, 1.29–2.74), and self-reported disability (adjusted OR, 2.90; 95% CI, 1.63–5.15) (Vanderploeg et al., 2007). Vanderploeg et al. (2003) used the same sample but divided it into two groups: 626 veterans who had mild TBI (373 with no LOC and 253 with LOC) and 3,896 veterans who had no TBI (normal controls). Using logistic regression, they examined factors predictive of work status in each group. Demographic, medical, and psychiatric factors accounted for about 23% of the variance in the mild TBI group and about 13% of the variance in the normal controls. The authors conclude that the findings indicate that those factors have a greater influence on work outcome in those with self-reported mild TBI than in those without. It is not clear whether the self-reporting method of ascertaining mild TBI since military discharge (a period of about 16 years) influenced the findings.

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Independent Living

A few secondary studies examined living situations after TBI (Dikmen et al., 1993; Kersel et al., 2001; Engberg and Teasdale, 2004). The results have indicated that at least for the first few years after injury, the predominant change is that many people who lived independently before the injury lived with parents after the injury. Dikmen et al. (1993) reported on a group of 22 of a sample of 31 moderately to severely injured subjects who were living independently before injury and were followed up to 2 years after injury. At 1 year after injury, 50% were living independently, 45% were living with parents, and 1 person (5%) was in a nursing home. By 2 years after injury, 68% were living independently, 27% were with parents, and 5% were in a nursing home. In comparison, only 6% of friend controls who lived independently 1 year before were living with parents. Kersel et al. (2001) reported similar findings in a group of severe-TBI patients at 6 months and 1 year after injury with the pattern showing a decrease in living alone or in flats from before to after injury and an increase in living with parents after injury. Engberg and Teasdale (2004) compared living situation before injury with living situation 5, 10, or 15 years after injury in a group of TBI patients who sustained cranial fractures and a group who suffered cerebral lesions. They found that the most frequent change in both groups was that most of those who had lived with parents before injury were living alone or with partners.

The results from the Dikmen et al. (1993) and Kersel et al. (2001) studies on independent living are consistent with those reported in the primary studies, except for the study by Engberg and Teasdale (2004) which may have been due to a number of factors including milder injuries in the sample, or people living in nursing homes or other sheltered environments not responding to the recruitment efforts.

Social Relationships

None of the secondary studies was devoted primarily to this topic, but some papers included information on social integration after TBI (Dikmen et al., 1993, 2003; Engberg and Teasdale, 2004; Kersel et al., 2001; Vanderploeg et al., 2007; Walker and Eruclei, 1969; Whiteneck et al., 2004). Most studies have found that social relationships suffer after TBI, although this finding has not been entirely consistent (Walker and Erculei, 1969; Vanderploeg et al., 2007). For example, Kersel et al. (2001) described social contacts before and 6 months and 1 year after injury of 65 people who sustained severe TBI. Although 95% of the sample reported that they had visits from friends before injury, the percentage had dropped to 62% at 6 months after injury and to 59% at 1 year after injury. Likewise, visits to friends went from 100% before injury to 76% and 75% at 6 months and 1 year after injury, respectively. Visits to family also decreased from 94% to 70% and 68%. The measure that showed the least decline was maintenance of good family relationships: 98% before injury and 94% and 90% after. Engberg and Teasdale (2004) examined social interaction in subjects with TBI who sustained cranial fractures and a group that suffered cerebral lesions 5–15 years earlier. They report that 18% of the cranial-fracture group and 48% of the cerebral-lesion group said that life with cohabitants had changed from before injury, and 12% and 37% said that they were seeing other family or friends somewhat or much less than before. Dikmen et al. (1993) examined 31 moderately to severely injured adults 1 and 2 years after injury and compared them with 102 friend controls. They found the mean percentage dysfunction on the SIP (Bergner et al., 1976) Social Interaction

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Scale was 10% at 1 and 2 years after injury, significantly higher than reported by the controls ($p < 0.0001$). In another study, Dikmen et al. (2003) used the Social Integration Subscale of the Functional Status Examination (Dikmen et al., 2001) 3-5 years after injury with 210 patients who had complicated mild to severely injured TBI. About 10% said that they were socially isolated, with social interactions limited to parents, immediate family, or other residents; about 25% reported having partially limited social interactions (fewer friends, less contact with friends or family, or less ability to make new friends) or greater reliance on others to maintain social interactions; about 10% said that social interactions were not more limited but it was more difficult to get along with friends and family; and the remaining 55% said that social interactions were the same as they were before the injury. Whiteneck et al. (2004) conducted a population-based study of 1,591 adult TBI patients in Colorado and followed them to 1 year after injury. They reported that 22% of their sample showed handicap on the Social Integration Subscale of the Craig Handicap Assessment and Reporting Technique Short Form (CHART-SF) (Whiteneck et al., 1992). The percentage of subjects showing handicap on this scale varied significantly by TBI severity (34% of severely, 32% of moderately, and 20% of mildly; $p < 0.01$) and by age (10% showed handicap at the ages of 16–24 years, 21% at 25–44 years, 26% at 45–64 years, and 43% at 65 years or over; $p < 0.01$).

In contrast, Walker and Erculei (1969) reported that 87% of the 343 World War II veterans seen 14–17 years after TBI rated their social adjustment as normal and only 5% rated themselves as asocial. It is not clear whether more dysfunction would have been reported if questioning had been more detailed. Vanderploeg et al. (2007) examined satisfaction with social support and availability of social support in three groups of subjects from the Vietnam Experience Study that evaluated Army veterans about 16 years after military discharge: 3,214 subjects who said that they had not experienced an MVA or TBI since discharge, 539 subjects who said that they had been injured in an MVA but had not sustained a TBI, and 254 subjects who said that they had experienced a TBI with altered consciousness but were not hospitalized. The authors were unable to find any significant differences among the three groups on being very or somewhat dissatisfied with social support or having a decrease in the availability of social support. However, they did find that the mild-TBI group had significantly higher odds of not being married than the other groups (adjusted OR, 2.01; 95% CI, 1.57–2.75).

Leisure Activities

A number of secondary studies examined leisure and recreational activities after TBI (Dikmen et al., 1986, 1993, 2003; Engberg and Teasdale, 2004; Kersel et al., 2001). The results indicate that, with the possible exception of people with mild TBI, leisure and recreational activities appear to have been disrupted after injury and the disruption continued to be a problem many years after injury. For example, Kersel et al. (2001) reported that in their sample of 65 patients with severe TBI the percentage who were participating in leisure activities decreased from 95% before injury to 62% at 6 months and 70% at 1 year after injury. Engberg and Teasdale (2004) examined the effect of the injury on leisure activities in a group of subjects with TBI who had sustained cranial fractures and a group who had suffered cerebral lesions 5–15 years earlier. They found that 21% of the cranial-fracture group and 51% of the cerebral-lesion group reported some or marked disruption in leisure activities. Dikmen et al. (1986) examined resumption of leisure and recreational activities in 19 persons with mild TBI. At 1 year after injury, 12 had resumed the activities with no limitations, and six with limitations; 1 person did

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not resume activities but this was not injury related. Dikmen et al. (1993) examined 31 moderately to severely injured adults at 1 and 2 years after injury and compared them with 102 friend controls on the SIP. Dysfunction on the SIP represents general health and injury related limitations. The mean percentage dysfunction on the SIP Recreation and Pastimes Subscale (Bergner et al., 1976) was 17% at 1 and 2 years after injury, which was significantly higher than the percentage in the control subjects ($p < 0.0001$) and one of the highest percentages on endorsed scales of the measure at 1 and 2 years after injury. Dikmen et al. (2003) used the Leisure and Recreation Subscale of the Functional Status Examination (Dikmen et al., 2001) on 210 people 3–5 years after complicated mild to severe TBI to assess leisure and recreational activity levels. About 15% said that they had dropped all or nearly all their leisure and recreational activities, about 35% had dropped or were helped with only some of their previous activities or were performing their leisure activities less frequently or for shorter periods, about 10% had not dropped any leisure activities but found them to be more difficult (for example, they tired more easily, lost balance or concentration, or performed less capably for any reason), and the other 40% reported that leisure activities were the same as before injury.

Functional Status

A number of secondary studies examined functional status after TBI, and the findings have indicated significant dysfunction regardless of how functional status is measured (Dikmen et al., 1993, 2003; Whiteneck et al., 2004; McCarthy et al., 2006; Colantonio et al., 1998; Livingston et al., 2005). For example, Dikmen et al. (1993) followed 31 moderately to severely injured adults 1 and 2 years after injury. They found significantly more ($p < 0.01$) endorsement of difficulties on the SIP (Bergner et al., 1976) in persons with TBI than in friend controls on all subscales at 1 and 2 years after injury except eating at 2 years after injury. The SIP Physical Summary Score showed a steeper drop in the first year than the SIP Psychosocial Summary Score. The SIP Psychosocial Summary Score also showed a decrease in the first year, but these problems continued to be reported more frequently at 1 and 2 years after injury than problems on the physical scale. In another study, Dikmen et al. (2003) followed 210 persons up to 3–5 years after complicated mild to severe TBI. They examined change in everyday life from before injury to 3–5 years after injury. Limitations were seen in all measures, with personal care and ambulation least affected and leisure, major role activity (such as work and school), and social integration most affected. The magnitude of difficulties was significantly related to the severity of injury ($p < 0.01$).

Whiteneck et al. (2004) conducted a population-based study of TBI in Colorado. They followed 1,591 adult TBI patients to 1 year after injury and reported on the results of the FIM instrument (Guide for the Uniform Data Set for Medical Rehabilitation, 2000) that evaluates disability and the CHART-SF (Whiteneck et al., 1992) that measures handicap or level of community integration. They found that 37% of the sample was scored on the FIM as needing the assistance of another person in physical or cognitive activities of daily living; the score varied significantly with severity ($p < 0.01$), a higher percentage of severely injured subjects requiring assistance. The FIM score also varied significantly with age, those 65 years old or older needing greater assistance than younger groups ($p < 0.01$), and with sex, more women than men needing assistance ($p < 0.01$). The total CHART-SF score indicated that 16% of the TBI subjects showed handicap. The percentages of cases showing handicap on the different subscales were as follows: 6% on physical independence, 16% on cognitive independence, 14% on

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mobility, 30% on occupation, 22% on social integration, and 25% on economic self-sufficiency. The total score and all subscales of the CHART-SF varied significantly with severity (each $p < 0.01$), with a higher percentage of subjects showing handicap in the more severely injured group than in the less severely injured groups. The authors also found that older people and women were more likely to show handicap. Livingston et al. (2005) examined the FIM at 1 year after injury in 236 subjects who had blunt isolated TBI defined as an AIS head score of 3 or higher and an AIS score for any other body area as no higher than 1. They examined severity of the injury and outcome by age group. The youngest group (18–29 years old) suffered the most severe TBI, but this group showed the best FIM score at 1 year. Patients older than 60 years old when injured showed the least improvement and had significantly lower FIM scores ($p < 0.05$) at 1 year. The authors concluded that the older patients made less recovery despite having less severe injuries than other age groups.

McCarthy et al. (2006) studied functional status with the Psychosocial Health Scales of the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) (Stewart and Ware, 1992) in a population-based study of hospitalized persons with TBI in South Carolina. Outcome data were collected on 1,825 subjects and weighted to represent the total number of TBI-related hospitalizations in South Carolina (7,612). At 1 year after injury, 29% reported poor psychosocial health, defined as a score less than 40, which represents more than 1 standard deviation below age- and sex-matched population norms. Colantonio et al. (1998) also reported that the greatest differences between data on their small sample of subjects seen 5 years after injury and normative data on the SF-36 were on items on the “mental health scale” and the “role limitations due to physical health scale”.

Quality of Life

A few secondary studies examined quality of life (QOL) after TBI (Whiteneck et al., 2004; Corrigan et al., 2001; Teasdale and Engberg, 2005; Engberg and Teasdale, 2004) and in general had results that indicated significant decreases in QOL. For example, Whiteneck et al. (2004) found that 29% of the persons with TBI in their population-based study of TBI in Colorado reported QOL that was fair or poor at 1 year after TBI. The percentage of subjects reporting fair or poor QOL varied significantly with TBI severity ($p < 0.01$): 42% with severe injury, 37% with moderate injury, and 26% with mild injury. Engberg and Teasdale (2004) found that a group of subjects with cranial fractures report significantly higher life satisfaction ($p < 0.01$) than a group with more severely cerebral lesions 5–15 years after injury. Teasdale and Engberg (2005) also examined subjective well-being and QOL with the European Brain Injury Questionnaire (Teasdale et al., 1997). They calculated averages on nine scales and converted them to z scores by using a Danish nonpatient norm sample of 64 adults from another study. The means in the less severely injured cranial-fracture group were never significantly worse than the norms, but the means in the cerebral-lesion group indicated substantially worse QOL. Subjective well-being was similar in the sample queried at 5 years, 10 years, or 15 years after injury; that is, it did not decrease or improve as a function of the length of the followup period. Corrigan et al. (2001) also reported a minimal change in life satisfaction in their longitudinal sample seen at 1 and 2 years after injury.

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Functioning of Relatives

Several secondary studies examined the emotional and social functioning of relatives of persons with severe TBI (Livingston et al., 1985; Marsh et al., 1998). Livingston et al. (1985) reported high levels of anxiety, psychiatric illness, and burden in relatives at 6 and 12 months after the injury. For example, 37% of their sample was anxious, according to the Leeds Anxiety Scales (Snaith et al., 1976) at both 6 and 12 months after injury. Psychiatric illness was found in 37% of their sample at 6 months and 28% at 12 months, as measured with the General Health Questionnaire (Goldberg, 1978). Marsh et al. (1998) studied 69 primary caregivers of severe TBI survivors at 1 year after injury. Their results showed that 32% had clinically significant depression, 35% had clinically significant anxiety, and 25% had impaired social adjustment. Machamer et al. (2002) examined the burden experienced by 180 relatives of people who had complicated mild to severe TBI at 6 months after the injury. Significant others reported both positive and negative aspects of caregiving. However, negative experiences and burden were systematically related to increased TBI severity, worse acute cognitive outcome, and other factors. For example, the RR of experiencing negative burden was more likely when GCS was 8 or lower (RR, 1.9; 95% CI, 1.1–3.4).

SUMMARY AND CONCLUSIONS

The committee reviewed 14 primary studies and 25 secondary studies of social function as an outcome after TBI. Depending on severity and acuteness, TBI can affect all aspects of functioning, including such activities of everyday life as personal care, ambulation, mobility, and higher-level psychosocial functioning—employment, social relationships, independent living, recreation, and so on.

TBI clearly has adverse effects on social functioning. Some of the impairments might be related to injuries to other parts of the body sustained at the time of TBI. However, those with moderate to severe TBI have more functional impairment than those with injuries to other parts of the body alone. In civilian populations with mostly closed TBI, employment (which has received the most research attention) is adversely affected. TBI decreases the probability of employment after injury in those who were workers before their injury, lengthens the timing of their return if they do return to work, and decreases the likelihood that they will return to the same position. Those adverse effects are related to the severity of injury as measured by neurologic severity indicators and even more to post-TBI neuropsychologic impairment. Although those with moderate to severe TBI are clearly affected, there is insufficient evidence on unemployment in those with mild injuries.

Penetrating head injury sustained in wartime clearly is associated with unemployment. The probability of being employed 15 years after the Vietnam War was related to the number of residual neurologic deficits, brain-volume loss, and cognitive status.

TBI also adversely affects leisure and recreation, social relationships, functional status, QOL, and independent living. By 1 year after injury, psychosocial problems appear to be greater than problems in basic activities of daily living. Although there is a dose–response relationship between severity of injury and those social outcomes, there is insufficient evidence to determine at what level of severity the adverse effects are demonstrated.

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The committee concludes, on the basis of its evaluation, that there is sufficient evidence of an association between sustaining a penetrating TBI and long-term unemployment.

The committee concludes, on the basis of its evaluation, that there is sufficient evidence of an association between sustaining a moderate to severe TBI and long-term adverse social-function outcomes, particularly unemployment and diminished social relationships.

The committee concludes, on the basis of its evaluation, that there is inadequate or insufficient evidence to determine whether an association exists between sustaining a mild TBI and long-term adverse social functioning, including unemployment, diminished social relationships, and decrease in the ability to live independently.

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TABLE 9.1 Social Function

Reference	Study Design	Population	Type of TBI	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
Schwab et al., 1993	From Vietnam Head Injury Study	520 Vietnam veterans with penetrating head injury sustained in 1967–1970 seen at WRAMC for about 15-year followup 85 uninjured controls recruited from VA who had served in Vietnam in same years and were in same age range	Penetrating head injury, majority low-velocity, shrapnel	Work status in relation to neurologic, neuropsychologic, social-interaction measures	Posttraumatic epilepsy, paresis, visual-field loss, verbal memory and reasoning loss, visual-memory loss, psychologic problems, self-reported violent behavior contribute to work status; Strong linear association between total number of residual disabilities, work status; brain-volume loss, post injury AFQT explained similar amount of variance in work status as number-of-disabilities model	Groups similar on age at re-examination, on AFQT taken before Vietnam	Nonworkers may have been overrepresented
Ommaya, 1996	Retrospective cohort	1,617 hospital admissions for TBI in 1992, 1993 4,626 hospital admissions for orthopedic or internal injury 9,997 random sample of active-duty Army population	Mean ISS for head injured group, 6.0 (median, 4.0); mean for head injured group fighting, 7.0 (median, 5.0); mean AIS head in head injured group not involved with fighting, 2.2 (median, 2.0); mean AIS head in head injured group fighting, 2.4 (median, 2.0)	Adverse action (disciplinary action recorded in personnel file), discharge from military service for behavioral criteria, criminal conviction, medical discharge compared in these groups	After adjusting for confounders, head injury increased risk of behavioral separation by 4 times compared with normals; head injury increased risk of criminal conviction 5 times compared with normals; head injury increased risk of post injury adverse action by 1.3 times compared with normals, decreased risk of medical discharge by 0.64 times compared with orthopedic group	Age, sex, marital status, educational level, pay grade, months in current grade, years of active-duty service, injury severity, preinjury adverse action	Alcohol use not investigated
Ommaya et al., 1996	Retrospective cohort	2,226 TBI discharged in 1992, examined in military hospitals compared with total	1,778 mild TBI (AIS head, 1 or 2) 174 moderate TBI (AIS head, 3)	Examined discharge from military service due to behavior, criminal	ORs, (95% CIs) for discharge from military service after TBI by level of severity compared with entire		

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Reference	Study Design	Population	Type of TBI	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
		discharge population (1,879,724)	274 severe TBI (AIS head, 4 or 5)	conviction, alcohol or drug abuse, medical disability	discharge population: Discharge due to alcohol or drug use: mild, 2.6 (1.6–4.3) moderate, 5.4 (1.7–16.9) severe, NS Discharge due to behavior: mild, 1.8 (1.4–2.2 moderate, NS severe, NS Discharge due to criminal conviction: mild, 2.7 (1.9–3.9 moderate, NS severe, NS Discharge due to medical disability: mild, 7.5 (6.0–9.3 moderate, 25.2 (16.2–39.2) severe, 40.4 (30.0–54.4)		
McLeod et al., 2004	Retrospective cohort	564 British Army personnel who had TBI in 1994 368 British Army personnel who had lower-limb fracture in 1994 (and no other injuries) 25,575 healthy Army subject All had served for ≥1 year before 1994, excluding basic training, and were fully fit before 1994	Selected if had ICD codes for TBI in absence of other injury codes; thus, all TBI admitted to hospitals or medical-center wards; those with milder injuries that did not require inpatient management not included	Employment retention for 6 years after TBI	Retention was examined by stratifying for age (16–24, 25–28, 29–33, ≥34 years), reflecting different career stages in Army Youngest Ss (16–24 years old): healthy Ss left Army earlier than Ss in either injury group; median survival times, healthy Ss 1.74 years, TBI Ss 3.91 years, lower-limb fracture Ss 4.39 years Oldest Ss (≥34 years old): healthy Ss served longest of 3 groups; median survival times		Length of service may have been confounder in that younger soldiers serving minimum term may be more like people who sustain TBI; type of employment could be confounder in that TBI would affect

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Reference	Study Design	Population	Type of TBI	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
					5.55 years, lower-limb fracture group 3.75 years, TBI group 3.33 years Subjects 34 years old or older had lowest employment retention: 69% in TBI group continued in Army beyond year 1, 19% still employed in year 6 (compared with 85%, 26%, respectively, of fracture group, 80%, 48%, respectively, of healthy group)		performance in different types of occupations
Dikmen et al., 1994 (Some subjects from Fraser et al., 1988 and McLean et al., 1993 included here)	Prospective cohort	366 head injured preinjury workers from 3 prospective longitudinal studies; mean age, 30 years; mean education, 12 years; 77% male, 89% white, 75% working >20 h/week before injury 95 TC; mean age, 31 years; mean education, 12 years; 75% male, 81% white, 78% working >20 h/week before injury	Hospitalized closed-head injury or penetrating injuries with evidence of head injury (any period of LOC, PTA >1 h, other objective evidence) at minimum Selection criteria varied among studies on inclusion of pre-existing conditions. Head injury severity 93 GCS <8; 56 9–12; 213 13–15	Time to return to work by TBI severity indexes, other system injury severity, demographics, preinjury information, neuropsychologic measures at 1 mo after	Dose–response relationship between TBI severity, time to return to work 6% returned to work by 1 year in those with TFC ≥29 days, 21% TFC 14–28 days, 46% 7–13 days, 67% 25 h–6 days, 67% 6–24 h, 82% <5 h, 87% in controls 26% GCS <8, 56% 9–12, 80% 13–15	Head injured, controls similar on demographics, preinjury employment status, types of jobs held Results presented as weighted averages	
Dikmen et al., 1995 (Includes subjects from	Prospective cohort	466 Ss with TBI (91% of original sample) from 3 prospectiive longitudinal studies; average age, 29.9	Severity mild to severe; both blunt and penetrating included; evidence of head injury (any	1 year after injury outcome on GOS, independent living, employment, income, sources of	Global outcome: TCs functioning significantly better on GOS than TBI at 1 year after injury ($p < 0.001$); more severe TBI related to	Dependent variables presented as weighted averages to	

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Reference	Study Design	Population	Type of TBI	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
McLean et al., 1993 and from Dikmen et al., 1994)		years; average education, 12 years; 73% male 124 TC who sustained bodily injury other than to head (94% of original sample); average age, 31 years; average education, 12 years; 71% male 88 FC, friends of TBI; 16–60 years old; no pre-existing conditions (86% of original sample); significantly younger (average age, 24.5 years; p < 0.0001) and had more education (average education, 12.5 years) than head injured group (p < 0.05)	period of LOC, PTA >1 h, other objective evidence) at minimum Selection criteria varied among studies on inclusion of pre-existing conditions, head injury severity	income, SIP	worse outcome on GOS; longer TFC (r, -0.63; p < 0.001), lower GCS (r, 0.49; p < 0.001), head injury-related complications (r, -0.38; p < 0.001), 1 or 2 nonreactive pupils (r, -0.30; p < 0.001), more limited and dependent; higher proportion in each head injured-severity subgroup rated as significantly more disabled than TC (p < 0.05) except TFC <24 h, GCS 13–15, or EDH Independent living: significantly fewer head injured living independently (76%) than TC (93%; p < 0.001); dose–response relationship with TBI severity (see Table 2 of Dikmen 1995, #2977), % living independently after injury (who were living independently before injury) TC 93%, TFC <1 h 89%, 1–24 h 89%, 25 h–6 days 74%, 7–13 days 49%, 14–28 days 55 %, >29 days 23% Employment: fewer head injured working at 1 year than TC (p < 0.05); increasing levels of head injury severity significantly related to decreasing % returned to work (p < 0.001) (Table 3 of	adjust for different selection criteria in 3 studies Examined possible confounding of results by basic demographics, litigation	

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Reference	Study Design	Population	Type of TBI	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
					Dikmen 1995, #2977), TC 63% working at 1 year, TFC <1 h 64%, 1–24 h 50%, 25 h–6 days 51%, 7–13 days 36%, 14–28 days 18%, >29 days 6%; significantly different from TC at 2 weeks or more ($p < 0.001$); no difference between head injured, TC on returning to school; no relationship with TBI severity Income: head injured earned significantly less in year after injury than TC ($p < 0.05$); as TBI severity increased, income decreased SIP: head injured report significantly more dysfunction than TC, especially on psychosocial ($p < 0.01$) (rather than physical) scales; increasing TBI severity related to more dysfunction reported on all scales except emotional behavior ($p < 0.01$) (see Table 4 of Dikmen 1995, #2977); SIP total mean score for TC, 6, significantly better than TFC groups 1 week or greater (7–13 days, 12, $p < 0.05$; 14–-28 days, 14, $p < 0.01$; >29 days, 17, $p < 0.001$)		
Doctor et al., 2005 (Also includes	Prospective cohort	418 TBI working before injury from 1 of 4 longitudinal investigations	Mild to severe; selection criteria varied among studies, but at	Working at 1 year after injury compared with expected	RR by sex, age group, educational level, 1-mo GOS, NP GCS:		TBI sample, normed comparison sample

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Reference	Study Design	Population	Type of TBI	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
some of the Ss in Dikmen et al., 1994; Dikmen et al. 1995; and Machamer et al., 2002)		enrolled in 1980–1994	minimum had any LOC, PTA >1 h or CT evidence of brain lesion	unemployment rates from Current Population Survey	13–15, RR, 3.46 (2.87–4.28) 9–12, RR, 4.85 (3.71–6.02) 3–8, RR, 5.98 (4.92–6.96) (dose–response relationship in terms of severity of TBI based on GCS)		overlapped only partially (1992–1994) Dose–response relationship in terms of severity
Oddy et al., 1978	Prospective cohort	54 closed-head injured (close relative also interviewed); 16–39 years old; PTA >24 h; admitted to 1 of 7 hospitals in Surrey, Sussex, or South-west London 35 controls with traumatic limb fractures and no head injury	48% PTA 1–7 days; 52% PTA >7 days; 90% road traffic accidents; 50% 16–20 years old, 80% <25 years old	Return to work, contact with friends, leisure activities, family life, marital relationships Compared before injury (as reported by relative within 1 mo of injury) with 6 mo after injury	Return to work 4–6 mo after injury of preinjury full-time workers: PTA 1–7 d, 71% full-time, 10% part-time PTA >7 d, 29% full-time, 21% part-time Controls, 63% full-time, 33% part-time R, 0.41 ($p < 0.003$) between PTA, length of delay in return to work Impairment of leisure activities: PTA 1–7 d, 33% PTA >7 d, 42% Controls, significant reduction ($p < 0.01$), % not reported Social contacts: PTA >7 d, decrease in number of friends ($p < 0.04$), single patients more dependent on parents ($p < 0.02$) No other significant differences Subjective symptoms: 77% closed-head injured >1 symptom, 35% >6 symptoms;	Closed-head injured, controls matched on age, socioeconomic status (not sex-matched)	Small samples

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Reference	Study Design	Population	Type of TBI	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
					65% reported poor memory or loss of temper or fatigue; number of symptoms had weak association with PTA (r, 0.30; $p < 0.02$) and time to return to work (r, 0.27; $p < 0.04$) Controls: 58% 0 symptoms, 20% >3 symptoms		
Edna and Cappelen, 1987	Prospective cohort	485 closed-head injured admitted in 1979–1980 to 3 general-surgery deptartmen. and 1 neurosurgery department in Trondelag, Norway; 15–64 years old at injury 89 controls admitted with acute appendicitis in 1979–1980	Closed-head injury with LOC, skull fracture, or intracranial hematoma; 89% GCS 13–15	Questionnaire on social, working outcome 3–5 years after injury; 85% response rate in closed-head injured, controls	Employment: Overall head injured: unemployed 12% before, 27% after Controls: 5% before, 16% after Unemployment rate increased more ($p < 0.01$) in closed-head injured than in controls More unemployment in those >45 years old (16% before, 53% after) than those <45 years old (11% before, 20% after) Social condition: Compared with before injury, rated as worse, same, or better than before, more controls than closed-head injured report contact with friends, family life, income better than before (each $p < 0.05$); more closed-head injured than controls report income same as before ($p < 0.05$); poor social outcome significantly related to unemployment (X^2,	None	No information on demographic comparison of closed-head injured, controls

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Reference	Study Design	Population	Type of TBI	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
					39.81; p, 5 x 10^{-8}), number of new postconcussion complaints (X^2, 73.19; p, 1 x 10^{-10})		
Gerberich et al., 1997	Case–control	99 undergraduate students at University of Minnesota hospitalized with brain injury in 1980–1984, 17–27 years old 198 matched uninjured controls with no documented injury requiring hospitalization during study period 121 injured controls hospitalized in same trauma centers as cases for injury other than brain injury during same study period	Defined as any injury above C-1 that resulted in LOC and/or loss of awareness and/or functional impairment; included penetrating and blunt forces resulting in concussion, contusion, hemorrhage, or laceration of brain or brain stem; 90% with mild TBI based on GCS; based on AIS head: 77% mild (AIS 1 or 2), 12% moderate (AIS 3), 11% severe (AIS 4 or 5)	Mean total credits attempted per quarter; mean GPA credits attempted per quarter; percentage of attempted credits completed; GPA Return to school	No differences when total groups (males, females) compared; significant before-injury to after-injury decrease in GPA in female cases compared with uninjured academic controls ($p < 0.02$) Comparison of female brain-injured cases and academic controls on nonattendance after injury: OR, 4.47 (1.21–17.13) Comparison of female brain-injured cases and injured controls on nonattendance after injury: OR, 1.14 (0.32–4.09) Brain-injury cases: neurologic deficits at discharge among total brain-injured cases, relation to post injury nonattendance, OR, 7.43 (1.22–48.37); upper-limb motor deficits associated with post injury nonattendance, OR, 11.29 (1.55–68.65)	Uninjured controls, TBI matched at 2:1 ratio to cases by age (±1 year), sex, academic progress classified as <90 or ≥90 total course credits Injured controls not matched to cases	Females with brain injury who returned to school had lower GPA, attempted fewer classes than academic and injured controls Failure of females to return to school associated with injury but not specific to brain injury
Stulemeijer et al., 2006	Retrospective cohort	299 mild TBI 18–60 years old admitted to ED level 1 trauma center in Netherlands; 89 sustained additional injuries	Mild TBI defined as impact to head with or without LOC ≤30 min, with or without PTA, hospital	6 mo after injury: Rivermead Post-Concussion Questionnaire; SF-36 physical functioning, social	Change in work: 35% mild TBI with additional injuries, 14% isolated mild TBI, 2% of controls report change in work ($p = 0.0001$) SF-36: all 3 scales	Analyses adjusted for age, sex, AIS head score	52% of mild-TBI sample, 61% of control sample completed questionnaires

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Reference	Study Design	Population	Type of TBI	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
		defined as AIS ≥2 in 1 or more other AIS–ISS body areas; mean age, 36.12 years; 75% male 261 controls went to ED for ankle or wrist distortion; mean age, 33.2 years; 45% male Mild TBI significantly older ($p < 0.01$), more were male ($p = 0.0001$) than controls	admission GCS, 13–15 Mild TBI with additional injuries had more severe TBI than those with isolated injuries (for example, more report PTA (78% vs 64%; $p < 0.05$), RA (47% vs 27%; $p < 0.01$), more frequent brain CT abnormalities (24% vs 14%; $p < 0.05$), worse AIS head score (mean, 2.3 vs 1.9; $p = 0.0001$)	functioning; GOSE; SF-36 perceived health change, change in work (defined as loss of work or change in work status to fewer hours or other lower-level job due to accident)	significantly different between groups (each $p = 0.0001$); post hoc tests show mild TBI with additional injuries have more dysfunction than isolated mild-TBI cases, both have more than minor-injury controls (each post hoc $p < 0.001$) Location of additional injuries significantly related to SF-36 physical functioning ($p < 0.01$); those with multiple injuries, injuries to extremities, or injuries to chest or abdomen report more problems; more dysfunction in severe injuries (ISS > 15) on physical functioning ($p < 0.01$) but no difference on other outcomes		
Heitger et al., 2007	Prospective cohort	37 mild closed-head injured; mean age, 29.1 years; mean education, 13.6 years; all employed or in school, none involved with litigation; excluded Ss if any evidence of alcohol or drugs at time of injury or regular use of psychoactive drugs or history of drug abuse or if had pre-existing neurologic or	Mild closed-head injury based on first assessed GCS of 13–15 without decreasing below 13 at any time in hospital; PTA <24 h in all cases	RHIFQ, SF-36 at 6, 12 mo after injury	SF-36: no significant differences between mild closed-head injured, controls on SF-36 at 6, 12 mo RHIFQ: not administered to controls; 27% mild closed-head injured report mild or worse change on one or more activities at 6 mo, 23% report mild or worse change at 12 mo; 49% at 6 mo, 61% at 12 mo report no changes compared with before injury on any activity	Controls matched to mild closed-head injured on age, sex, years of education	

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Reference	Study Design	Population	Type of TBI	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
		psychiatric problems or history of prior head injury with persisting symptoms 37 controls selected from volunteer database, matched to closed-head injured on age, sex, education; some recruited from relatives and friends of closed-head injured if match in database could not be found; same exclusion criteria as in closed-head injured group					
Bond and Godfrey, 1997	Cohort (consecutive hospital admissions)	62 blunt trauma subjects (55 men and 11 female) Consecutive hospital admissions to Neurological unit of Dunedin Pubic hospital between January 1985 and December 1988 All patients were discharged in a conscious state. 25 Orthopedic controls (20 men and 7 females) hospitalized for less than 1 week with	Subjects: blunt trauma associated with PTA exceeding 24 hours; mean duration of PTA was 14.98 days with a range of 1-61 days. 32% of cases had a duration of PTA of 1-7 days; 56% PTA 8-28 days; 12% PTA >28 days. 58% GCS >9 on admission;	Measure of pragmatic speech Conversations assessed between 6 months and 3 years post-injury.	Conversations with TBI patients were rated as significantly less interesting, less appropriate, less rewarding and more effortful than the orthopedic controls. Further the TBI patients' conversations were characterized by differences in the frequency of prompt usage and turn duration. TBI subjects were perceived to be less socially rewarding as a result of changes in their social behavior.	One way analyses of variance (ANOVAs) indicated that the mean scores of the different groups were not significantly different. Matched on age; sex; mean premorbid IQ	Excluded from participation in subjects and controls: premorbid history of psychiatric disorder; neurologic disease; alcohol dependency; or previous moderate to severe head injury. Also excluded were subjects younger than 15

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Reference	Study Design	Population	Type of TBI	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
		injuries typically associated with rapid recovery.	39% GCS 6-8; 3% GCS 4-5. 80% of cases had injury caused by road accident; 14% injury from a fall; 3% assaults; 3% blows from moving objects.				or older than 65. Five subjects who had PTA > 10 weeks were excluded.
Friedland and Dawson, 2001	Prospective cohort	64 TBI from MVA 19–58 years old, admitted to tertiary-care center in Toronto, Canada; 61% male; average ISS, 21; average LOS, 19 days; English-speaking 35 with no TBI but in MVA (defined as GCS of 15, no documented LOC or PTA, normal CT, if done, no documentation in chart regarding brain injury); age 19–58 years; 64% male; average ISS, 18; average LOS, 22.71 days; English-speaking Excluded anyone with severe disfigurement, amputation, spinal-cord injury	Mild TBI; initial GCS $\geq$13 (after 30 min); LOC $\leq$30 min or PTA $\leq$ 24 h	SIP, Reintegration to Normal Living Scale, return to work 6–9 mo after injury; also examined PTSD with Impact of Event Scale and General Health Questionnaire	SIP: mild TBI: overall mean, 20.80; psychosocial summary score, 21.14; physical summary score, 15.0; no mild TBI: overall mean, 15.09; psychosocial summary score, 10.86; physical summary score, 12.66; psychosocial summary score significantly different between groups (p = 0.01); no other significant differences Return to normal living: mild TBI mean, 69.23; no mild TBI mean, 73.91; not significantly different Return to work: 44% mild TBI returned, 41% no mild TBI returned; not significantly different; return to work examined by type of occupation grouped as independence and decision-making (including student, homemaker, professional or	Controlled for Time 1 (within 1 mo of injury) scores on PTSD for followup	Average ISS in both groups implies both groups suffered from serious other-system injuries, which may have influenced findings Counting students and homemakers as independent occupations may have influenced results because it may be easier for these Ssthan workers to return to their major activity after TBI

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Reference	Study Design	Population	Type of TBI	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
					semiprofessional, management), not independent (including clerical, sales, manual labor, skilled crafts, trade); mild TBI had significantly higher rate of return if job involved independence and decision-making (p = 0.004); no difference in rate of return by type of occupation in no mild TBI group PTSD: mild TBI had higher risk (p = 0.04; OR, 1.034; CI, 1.001-1.067); grouped Ss into definite PTSD (had qualifying scores on both measures of PTSD), possible (had qualifying scores on only 1 measure), none (did not qualify on either measure); percentage of mild TBI cases in expected direction, but no significant differences between mild TBI and no mild TBI		

Note: AFQT= Armed Forces Qualification Test, AIS = Abbreviated Injury Score, CDC = Centers for Disease Control and Prevention, CI = confidence interval, DVA = Department of Veterans Affairs, ED = emergency department, EDH = epidural hematoma, FC = friend controls, FIM = Functional Independence Measure, FSE = Functional Status Examination, GCS = Glasgow Coma Scale, GOS = Glasgow Outcome Scale, GPA = grade-point average, ICD=International Classification of Diseases, ISS = Injury Severity Score, LOC = loss of consciousness, LOS= length of stay, MCS = Mental Component Summary, MVA=motor-vehicle accident, NP = neuropsychologic, OR = odds ratio, PTA = posttraumatic amnesia, PTSD = posttraumatic stress disorder, RA = retrograde amnesia, RHIFQ = Rivermead Head Injury Follow-up Questionnaire, RR = relative risk, SIP = Sickness Impact Profile, SO = significant other, TBI = traumatic brain injury, TC = trauma controls, TFC = time to follow commands, WRAMC = Walter Reed Army Medical Center.

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10

OTHER HEALTH OUTCOMES

Traumatic brain injury (TBI) is an important cause of death worldwide and contributes to a considerable number of deaths and disability in the United States. The Centers for Disease Control and Protection has estimated that about 50,000 of the 1.4 million people who sustain a TBI in the United States will die as a direct consequence (NCIPControl, 2008). This section examines mortality and premature death in people who have a TBI.

MORTALITY AND TRAUMATIC BRAIN INJURY

PRIMARY STUDIES

Mortality and Traumatic Brain Injury in Military Populations

That head injuries reduce life expectancy has been posited since World War I. Medical records of Bavarian World War I veterans who were patients at a head-injury center were analyzed in 1964–1966 (Walker et al., 1971) (see Chapter 5 for a description of the military cohorts). The head-injury center was established in 1916, and many of the 5,500 men who sustained head injuries in World War I were followed for up to 50 years (Credner, 1930). About 1,000 records were randomly selected, and death certificates were sought from social-welfare offices in Bavaria and West Germany. Vital statistics were obtained for 647 cases and matched with those of 616 uninjured Bavarian World War I decorated veterans, who were able to be traced because they received pensions. Veterans were excluded if they were born before 1880 or died before the age of 35 years, if death dates were unknown, or if records were incomplete. Both penetrating TBI and nonpenetrating TBI were identified; posttraumatic epilepsy was also assessed. Compared with the general population of German men who were at least 35 years old in 1925, those with head injuries had 1.8% more deaths than expected. In 1965, 73% of the veterans with TBI had survived from the age of 35 years to the age of 65 years compared with 80% of those without TBI. Life expectancy of veterans with TBI was about 4 years shorter than that of those without TBI. Posttraumatic epilepsy had the greatest effect on life expectancy after the age of 50 years. Weiss et al. (1982) used data from the same cohort through 1972 to assess life expectancy and correlate it with the severity of injury. By 1972, 77% of TBI veterans (497 of 647) and 78% of control veterans (483 of 616) had died. When TBI was categorized as shallow

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(nonpenetrating or penetrating less 3 cm; 314 veterans) or deep (penetration greater than 3 cm, perforating wounds, or wounds of ventricle or brainstem; 283 veterans), those with deep wounds had slighter higher mortality between the ages of 45 and 60 years, but the difference was not significant ($p = 0.6$). Similar results were seen when cases were divided by severity of coma ($p > 0.6$).

Confirming the results of Walker et al., Weiss and colleagues (1982) found that mortality was nonsignificantly ($p = 0.08$) higher in older TBI veterans with posttraumatic epilepsy than in older TBI veterans without posttraumatic epilepsy; moreover, posttraumatic epilepsy had a marked effect in reducing life expectancy ($p = 0.01$) in veterans with TBI compared with control veterans. Men with TBI were more likely to die of cerebrovascular disease than the controls (19% vs 12%; $p = 0.01$), particularly men younger than 60 years old ($p = 0.015$), but that difference did not correlate with the severity of the TBI.

Corkin et al. (1984) continued work begun by Teuber and colleagues in 1948 on a cohort of 190 World War II veterans with penetrating TBI. Corkin et al. (1984) compared those veterans with a control group of 106 veterans who had peripheral nerve injury, matched for age at injury, years of formal education, and preinjury intelligence-test scores. As of 1983, 28.4% of the veterans with penetrating TBI and 17.0% of those with peripheral nerve injury had died—a statistically significant difference ($p = 0.03$). However, when veterans with head injuries were categorized by whether they had posttraumatic epilepsy, only those with epilepsy had significantly higher mortality than the controls ($p = 0.0002$). Such factors as the site of the brain lesion, age at injury, and preinjury and postinjury intelligence scores did not affect survival, although veterans with more education lived longer.

Rish and colleagues (1983) followed 1,127 male Vietnam veterans who had penetrating head injuries for 15 years. Over the 15-year period, 90 deaths (8%) had occurred: 46 in the first year after injury, nine during the second year, and then one to four per year. Most deaths occurred early in the first year after trauma and were the result of the injury or coma sequelae. After 3 years, compared mortality in the head-injured Vietnam veteran population approached the norm, according to actuarial projections for North American men 21–35 years old. Length of coma was the best predictor of long-term outcome, and posttraumatic epilepsy was not a significant factor in mortality in the first 15 years, although each seizure event carried its own inherent risk.

Mortality and Traumatic Brain Injury in Civilian Populations

Mortality in TBI patients can be studied from the time of injury, from the time of discharge from inpatient acute-care hospitals, or from the time of admission into or discharge from inpatient rehabilitation. Rates in cohorts of patients at those different points of entry into a study will be different. For example, rates in patients from the time of injury will be greatest because they include early deaths. In contrast, survivors of the acute phase who are studied during rehabilitation are likely to have lower mortality.

Mortality in Patients from Time of Injury or Admission into Acute-Care Hospitals

Brown et al. (2004) carried out a study to determine whether mortality from TBI was affected by the severity of the injury. Their population-based retrospective cohort study identified all Olmsted County, Minnesota, residents who had a diagnosis indicative of a potential

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TBI, and they reviewed the medical records from the Rochester Epidemiology Project for 1985–1999 (see Chapter 5). The review confirmed 1,448 cases of TBI—164 (11%) moderate to severe and 1,284 (80%) mild. There were 68 deaths in the moderate-to-severe TBI group. The Kaplan–Meier estimated 30-day case-fatality rate was 29.3% (95% CI, 22.0–35.9). The 68 deaths, compared with mortality in the 1990 Minnesota white population, were significantly more than the 12.8 expected (relative risk [RR], 5.29; 95% confidence interval [CI], 4.11–6.17); but the 14 deaths in those with moderate or severe TBI who survived for the first 6 months after injury did not differ significantly from the 12.7 expected (RR, 1.10; 95% CI, 0.60–1.85; $p = 0.72$). There were 78 deaths in the mild-TBI group, and the Kaplan–Meier estimated 30-day case-fatality rate was 0.2% (95% CI, 0.0–0.4). Over the full followup period, the 78 deaths were significantly greater than the 58.8 expected (RR, 1.33; 95% CI, 1.05–1.65; $p = 0.012$); but the 69 deaths in the people with mild cases who survived 6 months after injury were not significantly different from the 58.6 expected (RR, 1.18; 95% CI, 0.92–1.49; $p = 0.173$).

Mortality in Patients Discharged from Acute-Care Hospitals

Selassie et al. (2005) studied a representative sample of 3,679 TBI patients within a year of their discharge from any of 62 acute-care hospitals in South Carolina in 1999–2000 to document mortality within 15 months of discharge. Patients were stratified on the basis of TBI severity and hospital size. Of the sample, 3,371 (91.6%) were alive, and 308 (8.4%) had died within about 15 months of their discharge. Deaths were confirmed by using the Social Security Death Index (SSDI) and were classified as TBI-related or not. Of the 308 deaths, 17% were classified as TBI-related, and 63% of them occurred within the first 3 months after discharge, compared with 47% of the non–injury-related deaths. Findings indicate that the older the person, the higher the likelihood of early death. Males were more likely than females to die after TBI hospitalization if they were younger than 35 years old or older than 54 years old, but mortality was higher in females in the age range of 35–54 years. The authors also report that the severity of the TBI influenced mortality, as did the place of treatment. Patients who were treated in hospitals with trauma centers were less likely to die within 15 months after hospital discharge than patients treated in hospitals without trauma centers.

Mortality in Patients Admitted into or Discharged from Rehabilitation Centers

In a retrospective cohort study, Baguley et al. (2000) assessed mortality in 476 people who had sustained severe TBI over a 10-year period compared with an age- and sex-matched sample of the general Australian population. Patients with TBI, resulting primarily from closed head trauma due to motor-vehicle collisions, were admitted into a rehabilitation hospital 1986–1996. Twenty-seven of the 476 patients with TBI had died by August 1997, for a mortality rate of 5.7%. The median interval between injury and death was 17 months (range, 45 days–108 months after injury). Mortality in the TBI group was significantly associated with a lower level of functional independence on the basis of the Functional Assessment Measure ($p < 0.001$) slightly significantly with male sex ($p < 0.078$), with greater age (38 vs 32 years of age; $p < 0.055$), and with a premorbid psychiatric history ($p < 0.064$), but not significantly with a history of premorbid substance abuse ($p < 0.308$). In the general-population sample, the mortality rate was 1.5%. A Fisher's exact test indicated that significantly more people ($p < 0.001$) with TBI died (compared with the general population), with most deaths occurring in the first 12 months after injury. The leading causes of deaths were cardiorespiratory events (eight of 27) and infection (six of 27). The study is limited by the short followup period of about 5 years, the use

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of data from only one state in Australia, and the lack of functional assessment of and preinjury data on 52% of the deceased and 22% of the living TBI patients.

Harrison-Felix et al. (2004) studied 2,178 patients with moderate to severe TBI identified in the Traumatic Brain Injury Model Systems (TBIMS) national database, which covers 15 TBIMS rehabilitation centers. Most of the TBIs resulted from motor-vehicle crashes (62%) or acts of violence (20%). The study participants had a mean age of 37 years, 76% were men, 60% were white, and 37% had severe TBI on the basis of 24-hour postinjury Glasgow Coma Scale (GCS) scores. Using vital-status information obtained from the SSDI the authors identified 161 deaths in 2,178 people with TBI who were followed for 17 days–12.8 years after injury for a mortality rate of 7.4%. Compared with age-, sex-, and race-specific mortality rates for the general population, the authors found that individuals with TBI were at twice greater risk of death than those in the general population (95% CI, 1.69–2.31). The median interval between injury and death was 2 years; 38 of the 161 deaths occurred between rehabilitation discharge and 1 year after injury. Life expectancy was reduced by 5–9 years (average, 7 years), depending on age at injury, race, and sex.

Long-term survival of severely injured TBI patients was also studied by Ratcliff and colleagues (2005), who reviewed medical records of 640 TBI patients discharged from a rehabilitation hospital in Pennsylvania during 1974–1984 and during 1988–1989. Most of the injuries resulted from motor-vehicle crashes (66.6%), and falls were next most-common cause (16.4%). There were 464 males and 176 females in the TBI population, and their mean age was 37 years. Vital status as of 1997 was determined by using the SSDI. There were 126 deaths, for a standardized mortality ratio (SMR), relative to the expected mortality in the Pennsylvania population, of 2.78 ($p = 0.0001$). An increased risk of early death was associated with a known history of alcohol abuse (SMR, 6.10; $p = 0.0001$), substance abuse (SMR, 8.00; $p = 0.0264$), and other personal or social problems (SMR, 7.03; $p = 0.0001$). A criminal record or history of psychiatric disorder and years of followup did not modify mortality.

The studies by Brown et al. (2004) and Ratcliff et al. (2005) indicate that functional status at time of discharge from rehabilitation is a leading indicator of later survival time, although severity of injury and other demographic variables, such as age at time of injury, are not.

Shavelle and Strauss (2000) published two mortality studies of people with TBI who received services from the California Department of Developmental Services and survived at least 12 months after injury. The department serves the severely disabled, including those with developmental disabilities and those with long-term cognitive deficits. In nonambulatory patients, observed mortality exceeded expected mortality by a factor of 16.6 in 15- to 29-year-olds and 7.3 in 30- to 44-year-olds. In patients who were more ambulatory, the SMR was 2.5 for 15- to 29-year-olds who could walk with support or could walk unsteadily for at least 10 feet and 2.7 for those who could walk well alone for at least 20 feet.

SECONDARY STUDIES

The committee identified 12 secondary studies, as discussed below. Several studies used cohort designs to examine mortality in people who have TBI. The people studied have been only patients with TBI; that is, there have been no external comparison groups. The best of the studies

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have followed patients from the time of TBI. Others have examined subsets of the universe of patients with TBI, such as those admitted into rehabilitation hospitals, in which case the more selective nature of the population (survivors of the acute period who enter rehabilitation) may lead to death rates different from that in the whole universe of TBI patients who survive the acute period.

Six population-based studies were identified; most found consistent results regarding TBI and increased mortality (Harris et al., 2003; Hukkelhoven et al., 2003; Engberg and Teasdale, 2004; Lu et al., 2005; Flaada et al., 2007; Winqvist et al., 2007;).

Using data from the Rochester Epidemiology Project (see Chapter 5), Flaada and colleagues (2007) compared the observed number of deaths after TBI with the expected number of deaths. Mortality within 6 months increased with age in both moderate and severe TBI cases. Mortality in moderate and severe cases was 40 times that in mild cases independently of age. Among those surviving at least 6 months, 10-year mortality differed from expected only in the adult cases.

Lu et al. (2005) studied mortality associated with TBI in 1984–1996 to determine whether mortality had been decreasing. The study population consisted of 1,839 severely head-injured patients, whose data were extracted retrospectively from the Traumatic Brain Injury Data Bank (635 patients), the Medical College of Virginia (382), and clinical-trial databases in the United States (822). People with penetrating head injuries and treatment groups in the clinical-trial databases were excluded. Of the 1,839 patients with severe TBI, 526 died, for a mortality rate of 28.6%. Over the period 1984–1996, mortality from severe TBI fell from 39% to 27%. After adjustment for a variety of factors—including age, admission motor score, and pupillary response—the difference remained significant ($p < 0.05$).

Engberg and Teasdale (2004) conducted a population-based study of 389 patients identified in the national hospital register in Denmark who had cranial fractures or traumatic cerebral lesions. The mortality rate was assessed 15 years or more after injury. The acute and subacute mortality rate was 27% in those who sustained cerebral lesions and 4% in those who sustained cranial fracture.

Harris et al. (2003) assessed mortality after head injury in 13,908 people identified through the New York State Trauma Registry from January 1, 1994, to December 31, 1995. The overall mortality rate in all age groups was 14.7% (range, 5.6–30.2%). The authors found an increased mortality rate with increased age: 10.9% at ages 0–30 years, 12.4% at ages 31–50 years, and 21.3% at age above 50 years.

Winqvist et al. (2007) assessed mortality related to TBI by using the Northern Finland Birth Cohorts. One cohort is made up of people born in 1966 in two provinces in Finland and followed over a 34-year period. The authors identified 457 subjects who sustained their first ever TBI during 1966-2000, 78.1% of whom had sustained mild TBIs, including concussions and skull fractures. Nearly 10% had sustained moderate to severe TBIs, including brain contusions, intracranial hematomas, and diffuse traumatic axonal injuries. The authors found that the annual mortality in people with TBI was 14 per 100,000. Mortality related to TBI accounted for 12% of the total mortality in this group.

Hukkelhoven et al. (2003) analyzed individual patient data from four prospective studies (three multicenter randomized clinical trials and one prospective series with closed TBI) to

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assess mortality and outcome related to TBI. The mean mortality rate ranged from 23% to 40% in the four studies; the mean proportion with an unfavorable outcome ranged from 43% to 60%. The authors found that mortality increased with age from 21% in those 35 years old and younger to 72% in those 65 years old and older.

Five secondary studies assessed mortality related to TBI in hospitalized patients (Miller and Jennett, 1968; Fearnside et al., 1993; Lai et al., 1998; Gomez et al., 2000; Pentland et al., 2005). Many of the study populations consisted of consecutive series of patients admitted to hospitals with TBI. The studies found consistent results regarding TBI and increased mortality.

Fearnside et al. (1993) conducted a prospective study of 315 consecutive patients with severe TBI admitted to Westmead Hospital in Sydney, Australia. Severe TBI was defined as a GCS of no more than 8 within 6 hours after injury or deterioration to this level within 48 hours after injury. The authors found that GCS was inversely related to mortality. The correlation coefficient between mortality and GCS was 0.418 ($t = 8.14$; $p < 0.005$).

Gomez and colleagues (2000) studied outcomes in a cohort of 810 patients with severe closed-head injuries who were consecutively admitted to a hospital in Spain in 1987–1996. Severe head injury was defined as a GCS at admission of no more than 8 or deterioration to this level 48 hours after injury. At 6 months after injury, the overall mortality rate was 50.3%. In general, older patients had worse outcomes: the mortality rate reached 77% in the subgroup of 142 patients over 55 years old, but it was 37.5% in patients 46–55 years old.

Miller and Jennett (1968) evaluated mortality in a consecutive series of 400 patients with depressed fracture of the skull who were treated in the neurosurgical division of the Institute of Neurological Sciences in Glasgow during 1956–1967. The authors found that the cases were associated with a significant increase in mortality ($p < 0.005$).

Lai et al. (1998) conducted a retrospective study to evaluate long-term outcomes related to severe TBI in 70 patients admitted to a surgical intensive-care unit over a 29-month period. At 1 year after injury, the overall mortality was 50%.

Pentland (Pentland et al., 2005) assessed mortality in a cohort of 1,871 patients with mild, moderate, and severe TBI admitted to a regional head-injury unit in Scotland between 1981 and mid-2002. Of the 1,871, 93 had severe TBI, 205 moderate, and 1,573 mild. Fifty-seven patients died during the initial admission into the unit (42 with severe TBI, eight with moderate, and seven with mild). During subsequent years, 340 patients died (six had severe TBI, 33 moderate, and 301 mild).

Studies in the Sports-Injury Literature

To study the influence of intense physical training on life expectancy, Bianco et al (2007) examined male athletes born in 1860–1930 who had been inducted into various halls of fame: baseball (154), ice hockey (130), tennis (83), football (81), boxing (81), track and field (59), basketball (58), swimming (37), and wrestling (32). Because boxing is characterized by repetitive blows to the head, numbers of bouts and rounds were scrutinized. Median life expectancy of all the samples was 76.0 years; boxers had the lowest median life expectancy (73.0 years), and no differences were found by number of rounds or bouts.

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SUMMARY AND CONCLUSIONS

There is clear evidence of increased mortality in the acute phase after TBI and for some time afterward in both military and civilian populations with moderate to severe TBI. In the military literature, posttraumatic epilepsy in patients who initially survive penetrating head injuries is associated with an increased risk of death and about a 5-year decrease in life expectancy. In the civilian literature, studies in Minnesota suggest that although there is clear evidence of increased mortality in the first 6 months after injury, there is no evidence of increased mortality in patients with TBI beyond 6 months, regardless of severity. Studies of the subset of more severely injured patients who survive initial hospitalization and require inpatient rehabilitation demonstrate a worse prognosis, consistent with the greater degree of residual compromise: mortality some 2–7 times higher than in age- and sex-matched comparison populations.

The committee has reviewed 10 primary studies and 12 secondary studies of TBI and mortality and has found consistent results.

The committee concludes, on the basis of its evaluation, that there is sufficient evidence of a causal relationship between penetrating TBI and premature mortality in survivors of the acute injury.

The committee concludes, on the basis of its evaluation, that there is sufficient evidence of an association between moderate or severe TBI and premature mortality in the subset of patients who are admitted into or discharged from rehabilitation centers or receive disability services

The committee concludes, on the basis of its evaluation, that there is inadequate/insufficient evidence to determine whether an association exists between surviving 6 months or more after sustaining a mild, moderate or severe TBI and premature mortality.

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TABLE 10.1 TBI and Mortality

Reference	Study Design	Population	Type of TBI	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
Baguley et al., 2000	Cohort composed of clinical case series	Patients with TBI admitted to Brain Injury Rehabilitation Service, Westmead Hospital, New South Wales, Australia, 1986–1996; cases had survived through admission into rehabilitation facility; comparison group: expected mortality in age- and sex-matched Australian population in 1997	Severe; 97% closed, 3% penetrating	Mortality by August 1997 (mean, 5 years after trauma; range, 8 mo–11 years after trauma); ascertained by New South Wales vital-statistics search	476 patients, mean duration of followup 64 mo; 97% closed head injury, 3% penetrating head injury; 62% MVC, 21% falls or hit by object, 12% assault, 4% sports-related 27 of 476 (5.7%; 95% CI, 0.037–0.083) dead (median, 17 mo after trauma; range, 45 day–9 years 2 mo after trauma); expected mortality rate, 1.5% (CI, 0.006–0.03) ($p<0.001$ by Fisher's exact test) Contributing factors: low FAM on discharge ($p < 0.001$), being male ($p = 0.078$), greater age ($p = 0.055$), prior psychiatric morbidity ($p = 0.064$), but not prior substance abuse ($p = 0.308$) by chi2 or t test Cause of death: cardiorespiratory arrest (30%),	None	Missing FAM, preinjury information on substance abuse, psychiatric history from patients admitted before 1990 on 52% of the deceased, 22% of the living; no multivariate analysis

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Reference	Study Design	Population	Type of TBI	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
					infection (22%)		
Brown et al., 2004	Population-based retrospective cohort from Rochester Epidemiology Project	Any Olmsted County, MN, resident with medically attended TBI, 1985–1999 (N = 45,831); random 15.7% sample of TBI patients (N = 7,175) reviewed; 1,448 met inclusion criteria; comparison group: age- and sex-specific 1990 white Minnesotans	Documented concussion with LOC; PTA; neurologic signs of brain injury and/or intracerebral, subdural, or epidural hematoma; cerebral hemorrhage or contusion; brain stem injury; penetrating head injury; skull fracture; or postconcussive syndrome Moderate or severe (11%): skull fracture, intracranial hematoma, brain contusion, penetrating head injury, brain stem injury, or severe complications (neurosurgery, CNS infection, subarachnoid	Vital status through 2002 from medical records, state death tapes	Age 35.3 years for moderate–severe, 26.8 years for mild; mean followup, 7.4 years Mortality in moderate–severe: 68 deaths in 164 cases; overall risk of death increased compared with expected, RR, 5.29 (95% CI, 4.11–6.71) by long-rank statistic; 30-day CFR, 29.3% by Kaplan–Meier, risk increased compared with expected, RR, 5.29 (95% CI, 4.11–6.71); 14 deaths in those surviving ≥6 mo, no increase in risk, RR 1.10 (95% CI, 0.60–1.85) Mortality in mild: 78 deaths in 1,284 cases; overall risk of death increased compared with expected, RR, 1.33 (95% CI, 1.05–1.65); 9 deaths in first 6 mo (CFR, 0.2%), no	Age, sex for mortality analysis; age, sex, year of TBI with Cox proportional-hazards model for comparison of moderate–severe vs mild	Unique database on medical care of county's entire population; cohort not generalizable beyond Olmsted County—few minority-group members (96% white), all care in only 2 institutions

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Reference	Study Design	Population	Type of TBI	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
			hemorrhage, hydrocephaly, CSF leak) Mild (89%): LOC, PTA, postconcussive symptoms, focal neurologic signs		difference from expected 69 deaths in those surviving 6 mo; risk of death not increased compared with expected, RR, 1.18 (95% CI, 0.92–1.49) Comparison of moderate–severe with mild: risk of death increased in first 6 mo, RH, 5.18 (95% CI, 3.65–7.30) by Cox proportional-hazards model; no difference ≥6 mo, RH, 1.04 (95% CI, 0.57–1.88)		
Corkin et al., 1984	Prospective cohort (World War II veterans assembled at NYU by Teuber in 1948)	All WWII veterans with penetrating head injury from Teuber series (n = 190); excludes few with nonpenetrating head injury; 106 WWII controls with peripheral nerve injuries matched for age, education, preinjury AGCT (85% of controls in Teuber series with such injuries)	Penetrating, at least 3 years after trauma	Mortality to 5/1/1983 as function of various factors	Mortality: 54 of 190 (28.4%) with penetrating head injury dead vs 18 of 106 (17.0%), significant difference by Kaplan–Meier (p = 0.03); those with PT epilepsy (N = 82) more likely to be dead than those without (N = 91) or controls (p = 0.0002); PT epilepsy (p = 0.003), lower education (p = 0.02) associated with death	Cox proportional regression adjusted for age at injury, years of education, difference in AGCT (preinjury vs 10 years after trauma)	Vital status could not be determined on only one subject (treated as alive); no cause-of-death data collected

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Reference	Study Design	Population	Type of TBI	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
					by Cox		
Harrison-Felix et al., 2004	Retrospective cohort from 15 TBIMS centers	2,178 TBI patients ≥16 years old completing inpatient rehabilitation in 1988–2000; sample is 2,140 who survived >1 year after trauma; comparison group: US age- and sex-specific mortality in 1994	Age 37.4 years, 76% male, 60% white Cause of injury: MVC, 62%; violence, 20%; falls, 16%; other, 2% Severity: 37% severe (24-h max GCS ≤ 8) ALOS: 21 days acute care, 30 days acute rehabilitation	Mortality from SSA Death Index through 2001	Mortality: 123 of 2,140; median, 2 years; overall, SMR, 2.00 (95% CI, 1.69–2.31); <1 year after trauma, 38 deaths; ≥1 year after trauma, 123 deaths, SMR, 1.95 (95% CI, 1.61–2.29); life expectancy, average reduction, 7 years, depending on age at injury, sex, race, with range 5–9 years Risk factors: higher age, unemployment at time of injury, higher DRS score at discharge	Age, sex, race in determining SMRs from federal statistics for 2000; Cox proportional hazards for those surviving >1 year	Maximum followup only 13 years, average 3.1 years from 1 year after trauma; 38% loss to followup; two of 17 centers did not participate, so sample less representative
Lewin et al., 1979	Retrospective cohort (same population studied in book by AH Robert, 1979, with same results, but also mentioned suicide as cause of increased	7,000 consecutive head injured patients admitted into John Radcliffe Infirmary, Oxford, 10–24 years earlier (1955–1969); of these, 479 amnesic or unconscious >1 week; additional selected series: 64 cases unconscious >1 mo admitted to this or other facility	Severe in large part closed, but complicated by compression or penetration (traumatic or surgical for internal decompression) for 77 and 14, respectively, of 331 survivors	Vital status; for 178 (consecutive series), 28 (selected series) who died, cause of death; for 331 survivors, neurologic examination (all), test of cognitive function (217)	Overall mortality, 178 of 469 (38%) Life expectancy for four neurophysical-disability patterns—"decerebrate dementia": most <1 year, one >10 years; "athetoid pseudobulbar": reduced only by epilepsy, drowning, inhalation of food,	Age, maximum central neural disability score, maximum mental disability score, duration of PTA for model	Only 2% loss to followup; developed model for predicting long-term outcome on basis of age at injury, worst category of mental and neurophysical disability, length of PT amnesia in selected series

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Reference	Study Design	Population	Type of TBI	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
	deaths) (Cause-of-death comparison)	3–25 year earlier (including 24 from first set); causes of death in 78 patients discharged from initial hospitalization alive were compared with causes of death in general population of England, Wales in 1960 (not age- or sex-adjusted)			suicide; "brain-stem cerebellar" or "minor hemiparetic": reduction of <5 years Cause of death among those discharged compared with general public: meningitis, $p < 0.001$; epilepsy, $p < 0.001$; drowning, $p < 0.001$; respiratory, $p < 0.005$ Neurologic outcomes at 10 years (consecutive series): 11 (4%) totally disabled; 66 (14%) severely disabled, precluding normal social, occupational life; 214 (46%) recovered; 178 (38%) dead Hospitalization: continuing need discussed but not quantified		
Ratcliff et al., 2005	Retrospective cohort	640 patients ≥14 years old with moderate to severe TBIs discharged 8–24 years after trauma from	Head injury identified by ICD-8 and -9 codes 800–801-9, 803–804.9, 850–854.9,	Mortality through 1997	Overall mortality: 128 (19.7%) deaths; SMR, 2.78; $p < 0.0001$ by Poisson regression	Age at injury, sex, education, marital status, race, cause of injury,	Subjects outside range of interest for age at time of injury: <18 years, 19%; ≥60 years, 13%

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Reference	Study Design	Population	Type of TBI	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
		Pittsburgh, PA, rehabilitation center, 1974–1984, 1988, 1989; comparison group from Pennsylvania vital-statistics tables	excluding comorbid spine injury Cause of injury: MVC, 66%; violence, 2%; falls, 16%; other, 15% Moderate to severe cases (range, 4–54) retained, severity based on ICD at discharge as converted into ISS with range 0–75 (MacKenzie et al., 1989; Kingma et al., 1992).		Any preinjury social or behavioral problem: SMR, 5.82, $p < 0.0001$ Alcohol abuse: SMR, 6.10; $p < 0.0001$ Substance abuse: SMR, 8.00; $p < 0.0001$ Other personal or social problems: SMR, 7.03; $p < 0.0001$ Functional limitations at discharge (seven items with three levels): Bathing, $p = 0.01$; grooming, $p = 0.002$; dressing, $p = 0.011$; eating, $p = 0.003$; bed-to-chair, $p = 0.035$; toilet use, $p = 0.017$; walking across room, $p = 0.019$; summation partitioned into four levels, $p = 0.008$ Years after discharge, severity of injury not significant; final	severity of injury	Followup, 8–24 year after trauma; excluded 1985–1987 to keep sample size smaller, manageable; 6.5% could not be traced (assumed alive); univariate analysis of numerous variables, but final multivariate model contained only preinjury behavioral problems, grooming or eating problems; importance of preinjury factors suggests that a property of people experiencing TBI, rather than TBI itself, may increase mortality

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Reference	Study Design	Population	Type of TBI	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
					stepwise regression model if no preinjury behavioral problem or functional limitation at discharge, SMR, 1.69		
Rish et al., 1983	Prospective cohort (registry established 1976–1980 by MFUA, WF Caveness)	1,127 male Vietnam veterans alive 1 week after trauma; comparison group: age- and sex-matched from North American actuarial data (American Council of Life Insurance)	Penetrating cerebrocranial wounds	Mortality 15 years after trauma	Overall mortality: 90 of 1127 (8%), 46 in first year after trauma, 32 in first 3 mo, 16 in first month; compared with North American males, mortality increased up to 13 years after trauma (primarily 1–2 years after trauma), near actuarial rates at 14–15 years after trauma Cause of death: after second year, same as general population plus continuing losses due to coma sequelae, seizures and brain abscesses; coma (initial level of consciousness and duration) most predictive of mortality, not PT seizures 26 of 1,050 (2.6%)	Age and sex	Exclusively penetrating injuries, whose consequences may differ from those of concussive injuries

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Reference	Study Design	Population	Type of TBI	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
					deaths among those who were discharged to self care vs 67 of 80 (84%) of those who required continued hospitalization		
Selassie et al., 2005		3,679 patients ≥15 years old with TBIs discharged from 62 acute-care nonfederal hospitals in South Carolina in 1999–2001, with selection from 6,583 eligible stratified on severity, hospital size; comparison group: rates, causes of death in US population in 2000	AIS scores of severity converted from ICD-9-CM codes at discharge; mild, AIS ≤2); moderate, AIS 3; severe, AIS ≥4	Mortality <15 mo after discharge from acute care	Mortality <15 mo of discharge: 308 deaths; median, 93 days; range, 1–453 days; survival curves differ by severity, p < 0.0001 Overall SMR, 7.1 (95% CI, 6.3–7.9); cancer (n = 31), SMR, 3.1 (95% CI, 2.1–4.2); heart disease (n = 50), SMR, 3.7 (95% CI, 2.8–4.8); unintentional injury (n = 61), SMR, 36.3 (95% CI, 27.8–46.0); cerebrovascular disease (n = 18), SMR, 11.7 (95% CI, 8.2–15.9) Risk of death associated with age, number of comorbidities, AIS ≥ 4, Medicare, care in nontrauma center	Age, sex, race for SMRs based on US population; Cox proportional-hazards model	Some subjects <18, >60 years old Focus on only 15 mo after discharge 1,544 (42%) refused or not located Death certificates obtained for 94% of known deaths 74% of injury-related deaths related to original TBI Did not find excess deaths associated with seizures, respiratory infections, choking and suffocation, suicide

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Reference	Study Design	Population	Type of TBI	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
Shavelle et al., 2000	Retrospective cohort	2,629 people with TBI >15 years old, in 1988–1997, receiving services from California Department of Developmental Services (implying severe disability) and survived ≥1 year; comparator: 1990s US life tables by sex,	TBI by ICD-9 codes 800–804, 850–854	Mortality as recorded in state vital statistics	Mortality ratio: overall, 277%; nonambulatory patients, 660%; partially ambulatory, 196%; ambulatory, 180%	Stratified by ambulation status	Patients with severe disabilities only, not analogous to incident cohort
Walker et al., 1971	Cohort	1,000 Bavarian head injured men from WWI randomly selected from among 5,500 cases in head injury center in 1916–1927 with "sufficient information for analysis" of nature of injury; 1,000 unwounded Bavarian WWI veterans on pension lists for receiving medal; all born 1880–1900; final, 555 cases, 563 controls	Mixed severity, type (nonpenetrating slightly >50%)	Mortality to 1965 by life-table analysis; epilepsy at "some time after injury" (first event for most within year of injury, but persisted for most); broad classifications of cause of death	5-year bands of age-specific life expectancies calculated for >35 years; 73% of cases, 80% of controls alive at age 65 years; across all age bands, life expectancy was increasingly lower for control veterans, head injured without epilepsy, head injured with epilepsy in comparison with general population; aside from sequelae of injuries, no cause of death stood out for head injured	PT epilepsy; bracketing estimates derived by assuming that those with unknown vital status were all alive or were random sample of population	50 years of followup; statistics rather primitive; biases likely in selection of study population (for example, representativenes s of cases at center of all head injured and of those with sufficient information of all cases; controls all received medals); vital status of 400 of 1,000 not attainable, but same number found for

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Reference	Study Design	Population	Type of TBI	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
							controls;.for both groups, date, cause of death found for 56%, but vital status unknown for about one-fourth
Weiss et al., 1982	Cohort	1,010 head injured Bavarian men from WWI; 1,000 unwounded Bavarian WWI veterans; final, 647 cases, 616 controls		Mortality to 1972 by life-table analysis; cause of death.	Mortality: overall, 497 of 647 with TBI vs 483 of 616 controls; ages 35–70 years, brain-injured vs control, no difference; wound ≥3 cm vs 0–3 cm, ns increase; coma ≥1 day vs <1day, no difference; PT seizures vs no, increase maximal at ages 50–65 years; PT seizures vs control, increase (p = 0.01) Cause of death: TBI vs control, cerebrovascular (p = 0.01), <60 years (p = 0.015), ≥60 years (p = 0.04), not related to three measures of severity; cardiovascular–renal, no difference	None	If this sample was first defined in or before 1930, it has proved to be effectively a prospective cohort with 60 years of followup

NOTE: AGCT = Army General Classification Test, AIS = Abbreviated Injury Scale, ALOS = average length of stay, CFR = case-fatality rate, CI = confidence interval, CNS = central nervous system, CSF = cerebrospinal fluid, CT = computed tomography, FAM = Functional Assessment Measure, GCS = Glasgow Coma Scale, GOS = Glasgow Outcome Score, ICD = International Classification of Diseases, LOC = loss of consciousness, MFUA = Medical Follow-Up

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Agency, MVC = motor-vehicle crash, NYU = New York University, PT = posttrauma, PTA = posttraumatic amnesia, RH = relative hazards, RR = relative risk, SMR = standardized mortality ratio, SSA = Social Security Administration, TBI = traumatic brain injury. WWI = World War I.

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BRAIN TUMORS AND TRAUMATIC BRAIN INJURY

Brain tumors are growths of abnormal cells in the tissues of the brain and can be benign (noncancerous) or malignant (cancerous). The estimated number of new cases of brain and other nervous system tumors in the United States in 2008 is 21,810, and an estimated 13,070 related deaths are expected (NCI, 2008)

Gliomas, which are primary brain tumors, form in the glial cells of the brain or spinal cord and can spread throughout the nervous system. They can be benign or malignant. There are several types of gliomas, such as astrocytomas, ependymomas, and oligodendrogliomas. The committee examined several studies of brain tumors and TBI, and they are discussed in this section.

PRIMARY STUDIES

The committee reviewed 14 primary studies that examined the association between TBI and brain tumors. Most relied on self-reports of TBI to assess exposure. Three of the 14 studies—in Olmsted County, Minnesota (Annegers et al., 1979), Denmark (Inskip et al., 1998), and Sweden (Nygren et al., 2001)—used medical records to ascertain TBI and therefore are substantially less prone to recall bias.

In a retrospective cohort study, Annegers et al. (1979) followed 2,953 patients in Olmsted County, MN, who had a diagnosis of TBI during 1935–1974 to determine the occurrence of later brain tumors. Patients were selected from among 3,587 head-injured people in the population of Olmsted County who had survived the initial injury and had no history of pre-existing brain tumor. TBI was defined as brain involvement manifested by loss of consciousness (LOC), amnesia, or skull facture. Four brain tumors were observed in those with TBI, compared with an expected 4.13 (RR, 1.0; 95% CI, 0.3–2.6). There were one astrocytoma (SMR, 0.7) and three meningiomas (RR, 1.6; 95% CI, 0.3–4.7). The tumors were not associated with TBI severity and were diagnosed 5–16 years after the injury.

In a study of the incidence of brain tumors after TBI in Denmark (Inskip et al., 1998), nationwide registry of hospital discharges in 1977–1992 was used to identify 228,005 people who had been hospitalized for TBI on the basis of International Classification of Diseases-8 codes for fractured skull, concussion, or cerebral laceration or contusion. This registry was linked with the Danish Death Certificate File and the Danish Cancer Registry for 1977–1993 to determine the incidence of cancer. The incidence was compared with that in the Danish population to obtain standardized incidence ratios (SIRs), which were adjusted for sex, age, and calendar year. Concussion and fractured skull were the most common injuries and typically resulted from traffic accidents, falls, and sports-related activities. There were 299 tumors of the brain and nervous system in Denmark during the 7-year period, of which 261 were intracranial tumors, including 113 gliomas, 36 meningiomas, 12 neurilemmomas, eight medulloblastomas, and 16 vascular tumors. The SIR for any intracranial tumor associated with TBI was 1.36 (95% CI, 1.20–1.53), and most tumors occurred in the first year after the injury (SIR, 3.38; 95% CI, 2.59–4.34), regardless of tumor type. The SIR dropped closer to 1.0 in later years (SIR, 1.15; 95% CI, 0.99–1.32). Sixty-two intracranial tumors were diagnosed in the first year of follow up;

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43 of these were diagnosed during the first six months. The authors suggest that it is unlikely that the tumors grew quickly enough to be caused by the injuries and were more likely to have been undiagnosed tumors that were present when the injuries occurred and were detected in evaluation of the TBIs.

A similar retrospective study was conducted by Nygren et al. (2001) in Sweden. Records of patients hospitalized for TBI during 1965–1994 were linked with the Swedish Cancer Register, Cause of Death Register, and Emigration Register. Some 311,006 patients (192,090 men and 118,916 women) were followed for 3,225,317 person-years. TBI was defined as an ICD-7 or ICD-8 discharge code for skull trauma. There were 400 brain tumors during the period, but 119 that occurred in the first year after injury were excluded, and this left 281 cases of brain cancer (55 benign meningiomas; 161 primary brain tumors, including astrocytomas, glioblastomas, and gliomas; and 65 other brain tumors). When the patients were compared with the general Swedish population, the SIR was 1.0 (95% CI, 0.9–1.2) and did not vary substantially by tumor type, by age group, by severity, by sex, or by time since TBI.

Those three studies found that the incidence of brain tumors after severe head trauma was no different from the incidence in the general population if cases diagnosed in the first year after trauma were excluded. The other 11 studies used self-reports or self-reports of physicians' diagnoses to ascertain exposure. That creates some methodologic limitations because of the risk of recall bias, which would tend to overestimate risk, it does allow exploration of milder TBI than the large, registry-based studies. These are listed below in order of first author's names.

In a case–control study to identify environmental causes of brain tumors, Burch et al. (1987) assessed exposures in 215 people who lived in Toronto and southern Ontario and had brain tumors diagnosed in 1977–1981 and assessed in 1979–1982. Spongioblastomas, ependymomas, meningiomas, neuroepitheliomas, pituitary adenomas, neurilemmomas were excluded from the study. All subjects were individually matched to hospital-based controls by sex, area of residence, marital status, year of birth, date of diagnosis in the case of living patients, and date of death; controls were selected from the hospital nearest the residence of the subjects to reduce referral bias. None of the controls was admitted to the hospital for any type of cancer. Odds ratios (ORs) were calculated by using conditional and unconditional linear logistic regression models. Accidents and injuries were classified as having head involvement or not, and degree of injury was determined by whether medical attention was sought. Of those with brain tumors, 103 reported TBI compared with 41 controls, for an OR of 2.51 ($p < 0.0001$). When the subset of TBI that required medical attention was considered, the OR, 1.20, was not statistically significant ($p = 0.65$). The authors suggested that there was a potential for substantial recall bias in the reporting of TBI and that the risk disappeared when assessment was restricted to injuries that required medical attention.

The association between epilepsy, TBI, and brain tumors was assessed in a case–control study by Carpenter et al. (1987). Medical histories of about 66,000 workers employed in 1943–1979 at the Y12 nuclear facility at Oak Ridge, TN, or at the Oak Ridge National Laboratory were reviewed. Exposure was assessed by reviewing reports of TBI recorded in pre-employment medical histories or during employment that were in facility medical records. There were 82 fatal cases of primary malignant brain tumor (67 and 15 in white men and women, respectively) on the basis of review of death certificates. The authors compared the records of each of those cases with records of four controls matched for race, sex, facility, year of birth, and year of hire. Two (2.4%) of the 82 subjects reported having had a TBI compared with nine (2.7%) of the 328

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controls. The OR for brain cancer in those with a history of TBI compared with those without such injury was 0.9 (95% CI, 0.2–4.2); when the tumors were restricted to those of glial origin, the OR was 1.4 (95% CI, 0.3–7.2). The authors note that although the reports were documented, all the reported TBIs were self-reported and therefore subject to recall bias. Nonetheless, the recording of TBI at a time closer to the time of injury and for reasons unrelated to the study lessens the risk of recall bias.

Hochberg et al. (1984) studied the effect of TBI on the risk of glioblastoma in a case–control study of 125 patients with tumors and their self-chosen "best-friend" controls who were of the same sex and within 5 years of age. The subjects were derived from 231 patients, 15–81 years old, who had histologically confirmed glioblastomas in three hospitals in Boston, one in Providence, and one in Baltimore. The history of TBI was initially obtained by self-report but confirmed by interview. TBI was classified as severe (skull fracture or concussion followed by a complication, such as coma, intracranial hemorrhage, epilepsy, shock, or long-lasting impairment of memory, hearing, or vision) or mild (well-described concussion, brief loss of consciousness without any complications, or other inadequately described head trauma); other mild or poorly described head injuries were excluded. The OR for TBI was 2.1 (95% CI, 1.1–4.0); for mild TBI, 1.5 (95% CI, 0.7–3.3); and for severe TBI, 3.8 (95% CI, 1.3–11.0). If the TBI was sustained when the person was over 15 years old, there was an increased risk of glioblastoma, particularly in those over 50 years old at the time of the study and with severe TBI (OR, 5.1; 95% CI, 0.7–35.6). The age-adjusted OR for all ages was 1.4 (95% CI, 0.4–4.7) for mild trauma received after the age of 15 years and 10.6 (95% CI, 2.1–53.3) for severe trauma received at any age—a statistically significant trend ($p = 0.03$).

Hu et al. (1998) conducted a hospital-based case–control study of risk factors, including history of TBI, for astrocytoma and other glioma in residents of Heilongjiang province in northeastern China. Subjects were those with histologically confirmed gliomas (139 astrocytomas and 79 other brain gliomas) who presented for surgery in 1989–1995 at any of six major hospitals in the province. Two controls for each case (436 people) were selected from the same hospitals and were chosen from among those admitted for nonneoplastic or nonneurologic disease and matched for sex, age (within a 5-year interval), and area of residence. All study participants were asked about history of TBI that required medical attention and about diet, socioeconomic status, occupation, smoking, and other indicators of health status. A history of TBI was associated with increased odds of glioma (adjusted OR, 5.09; 95% CI, 2.51–10.31). Adjustments were made for income, education, number of years of drinking alcohol, occupational exposure, and consumption of vegetables and fruit.

A hospital-based case–control study in Rio de Janeiro, Brazil (Monteiro et al., 2006), found increased odds of brain tumors in adults who had experienced a TBI. The 240 subjects were 30–65 years old and had been hospitalized in the Brazilian national health system hospitals and had a diagnosis of primary brain neoplasms in 1999–2002. The 268 controls were age- and sex-matched inpatients in the same geographic region who had diagnoses of diseases other than brain tumor. Assessment of TBI was based on self-reports and had to have occurred at least a year before the diagnosis of the brain tumor (cases) or hospitalization (controls). TBI severity was based on whether hospitalization, LOC, or amnesia had occurred after the injury and on the number of injuries. Brain cancer was associated with prior TBI (OR, 1.49; 95% CI, 1.03–2.15), and the OR was adjusted for age, sex, schooling, epilepsy, and alcohol consumption. However, when analyzed by histologic type, clinical markers of severity (such as LOC and amnesia),

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numbers of episodes of TBI, and time since TBI, only having had more than one episode of TBI was associated with brain tumors (OR, 3.14; 94% CI, 1.50–6.61; p for trend, 0.004) and TBI 10–19 years before the diagnosis of brain tumor (OR, 1.31; 95% CI, 1.06–1.64). A dose–response relationship was observed according to the number of TBIs, particularly for meningioma (OR, 1.63; 95% CI, 0.96–2.75).

Phillips et al. (2002) conducted a case–control study in western Washington state in 1995–1998 to identify the risk of intracranial meningioma after TBI. For each of 200 people with intracranial meningioma (143 women and 57 men), they age- and sex-matched two controls. Cases were identified from the population-based Cancer Surveillance System, which included about 3 million residents. Each study participant was asked about a history of TBI, when it had occurred (by 10-year intervals), and whether it had resulted in LOC, hospitalization, or a visit to an emergency room. Subjects had increased odds of TBI (OR, 1.93; 95% CI, 1.28–2.62). The OR for intracranial meningioma in people with mild TBI was 3.23 (95% CI, 1.82–5.71); in people with severe TBI, 1.27 (95% CI, 0.82–1.98); in people with two or more TBIs, 2.75 (95% CI, 1.48–5.03); and in people who had TBI 10–19 years previously, 4.33 (95% CI, 2.06–9.10).

Preston-Martin and colleagues (1980, 1983) conducted a population-based, case–control study of intracranial meningioma in women and men in Los Angeles. All microscopically confirmed cases of meningioma were identified in the Los Angeles County Cancer Surveillance Program, and each subject was matched to a control residing in the same neighborhood by sex, race, and year of birth. Women who received a diagnosis in 1972–1975 completed questionnaires regarding risk factors; questionnaires were returned by 189 subjects and 185 controls. A history of medically treated TBI was a risk factor for meningioma (OR, 2.0; 95% CI, 1.2–3.5) and was independent of having had head or neck radiography. In another case–control study that focused on men with meningioma, 120 subjects who received a diagnosis in 1972–1979 were matched with 105 neighbor controls. TBI was associated with increased odds of meningioma if the person had ever participated in boxing as a sport (OR, 2.0; 95% CI, 1.1–3.2) or had a serious TBI that resulted in LOC or a permanent scar (OR, 1.9; 95% CI, 1.1–3.2). The authors noted that many of the men with TBI had not received medical treatment. In a later case–control study of the association between serious TBI—defined as resulting in a medical visit, LOC, or dizziness—and brain tumor in men, Preston-Martin et al. (1989) investigated cases of glioma and meningioma first diagnosed in 1980–1984 in Los Angeles County and identified in the Cancer Surveillance Program. The 272 subjects (202 with glioma and 70 with meningioma) were interviewed and were compared with 272 neighbor controls. To be included, serious TBI had to have occurred 2 years or more before the brain-cancer diagnosis. The OR for having had a serious TBI 20 years or more before was 0.8 (95% CI, 0.5–1.3) in those with glioma and 2.3 (95% CI, 1.1–5.4) in those with meningioma. Furthermore, the odds of meningioma, but not glioma, increased with the number of serious TBIs: with one TBI, 1.3 (95% CI, 0.6–2.9), with two TBIs, 2.1 (95% CI, 0.8–5.9), and with three or more TBIs, 6.2 (95% CI, 1.2–31.7).

Expanding the case–control approach internationally, Preston-Martin et al. (1998) used a standardized questionnaire to investigate risk factors for glioma and meningioma in six countries (two centers in Australia, one in France, one in Germany, two in Canada, one in Sweden, and one in the United States). Glioma and meningioma cases were in 729 men and 779 women who received diagnoses of either glioma or meningioma in 1984–1992 and were matched to controls by sex, age, and education. Participants were asked about medically treated TBIs, which were classified as serious if they caused LOC or amnesia or required hospitalization. Injuries were

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also classified as to whether they occurred 5–14 years, 15–24 years, or more than 25 years before the brain-cancer diagnosis. ORs for glioma or meningioma were not significantly increased in men who had had any TBI 5 years or more before diagnosis (OR, 1.18; 95% CI, 0.94–1.48 and OR, 1.49; 95% CI, 0.86–2.57, respectively) or who had had a severe TBI 5 years or more before (OR, 1.13; 95% CI, 0.87–1.48 and OR, 1.15; 95% CI, 0.57–2.34, respectively). There was no significant increase in the risk of either brain tumor in women regardless of TBI severity. Men had a slightly increased OR for glioma if they had sustained more than one TBI 5 years or more before (OR, 1.52; 95% CI, 1.00–2.32), but not if they had more than one TBI regardless of timing (OR, 1.67; 95% CI, 0.56–4.98). In men who had sustained their TBI 15–24 years before diagnosis, there was a statistically significant increase in the risk of meningioma (OR, 5.35; 95% CI, 1.72–16.62), but the increase was not seen in connection with other latent periods or in women.

In a study of primary brain tumors in residents of the Rein-Neckar-Odenwald area of Germany, Schlehofer et al. (1992) identified 226 cases diagnosed in two neurosurgical hospitals in January 1987–December 1988, of which 115 were histologically confirmed gliomas, 81 were meningiomas, and 30 were acoustic neuromas. The 99 men and 127 women, 25–75 years old, were interviewed during their hospital stay, as were 418 age- and sex-matched controls from the same residential areas as the cases. TBI that had occurred more than 5 years before and required a visit to a doctor were reported by 46 (20%) of the subjects and 113 (27%) of the controls (OR, 0.71; 95% CI, 0.5–1.1 for any brain tumor; OR, 0.70; 95% CI, 0.4–1.2 for gliomas; and OR, 0.52; 95% CI, 0.3–1.0 for meningiomas, adjusted for age and sex). The authors reported that there was no effect of having multiple TBIs or of varied latent periods, but the data to support these statements are not provided.

These 11 studies had mixed results. Eight found evidence of associations between history of TBI and later brain tumors, and four did not. The results of the four Preston-Martin studies suggest that the odds of meningioma are increased in people who have had a TBI, especially those with relatively remote histories (15 years or more before). That was also found by Phillips et al. and in a study with more heterogeneous histologic subtypes by Monteiro. Nonetheless, the findings of those studies are less compelling than the findings of the large population-based studies in Minnesota, Denmark, and Sweden primarily because of the potential for overascertainment of exposure among cases due to self-reporting of TBI. Nonetheless, it is notable that some well-conducted studies yielded a relatively specific association between TBI and risk of later meningioma as opposed to other tumor types and that some studies yielded a finding of a latent period of 10 years of more.

SECONDARY STUDIES

The committee identified two secondary studies that evaluated the relationship between TBI and brain tumors (Choi et al., 1970; Zampieri et al., 1994).

In a retrospective study (Choi et al., 1970) of patients with brain tumors in four University of Minnesota–affiliated hospitals in Hennepin County, Minnesota, there were 126 cases of histologically verified tumors diagnosed in 1963–1964. TBI was defined as a fractured skull, unconsciousness, or bleeding from the head that led to hospitalization or surgery. Controls were admitted to the hospitals for any condition other than tumors and were excluded if they had any neurologic, psychiatric, ophthalmologic, or lymphatic disorder; they were matched to cases

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by hospital of admission, sex, age, race, geographic area of residence, and locale of residence. No significant differences were seen in the frequency of TBI between the brain-cancer groups and their matched controls (OR, 0.83 for all verified central nervous system tumors; OR, 1.34 for all gliomas).

Zampieri et al. (1994) conducted a case–control study to assess risk factors related to brain tumors in 195 patients who presented with confirmed cerebral glioma in four neurosurgical departments in Italy. Controls were matched to cases on age, sex, date of hospitalization, and residence. A structured questionnaire was administered to assess education, occupation, environmental exposures, medical history, and history of TBI. TBI was classified as mild if LOC was brief and severe if LOC lasted for over 1 hour, and there were any related neurologic deficits, epilepsy, cranial fracture, or any neurologic procedure. The authors found no statistically significant association between malignant astrocytomas and history of TBI (OR, 0.5; 95% CI, 0.2–1.3). The study was limited in that there was a potential for substantial recall bias.

SUMMARY AND CONCLUSIONS

The committee reviewed 14 primary studies and two secondary studies of TBI and brain tumors and found mixed results. The three large population-based registry studies in Minnesota, Denmark, and Sweden found no association between TBI and risk of brain tumors, although the Danish study almost reached statistical significance. The Minnesota study was able to ascertain exposure up to 44 years earlier, and there were more than 3.2 million person-years of followup in the Swedish study. However, there is evidence from some of the other studies that there may be a weak but significant association between TBI and meningioma and that risk of brain tumors may be increased 10 years or more after TBI; this suggests the possibility of a long latent period before clinical presentation. The committee therefore does not believe that the possibility of an association between TBI and risk of later brain tumors is a closed question. It believes that longer-term followup, especially in large registry-based studies, is warranted to understand where there is measurable risk and, if it is increased, when and with what types of tumors it is most likely to be observable. For now, however, the committee concludes that the inconsistent results of the studies are most supportive of a classification of inadequate/insufficient evidence to determine whether an association exists.

The committee concludes, on the basis of its evaluation, that there is inadequate/insufficient evidence to determine whether an association exists between moderate or severe TBI and subsequent development of a brain tumor.

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TABLE 10.2 TBI and Brain Tumors

Reference	Study Design	Population	Type of TBI	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
Annegers et al., 1979	Double cohort	All TBI in Olmsted County, MN, 1935–1974' survived initial trauma; no known pre-existing tumor; comparator data from previous incidence study of brain tumors in Olmsted County	Head injury with LOC, PTA, or skull fracture	Brain tumors	Four brain tumors observed (three astrocytomas, one meningioma); RR (observed/expected) not significant overall or for two tumor types	None	TBI that did not reach medical care uncounted Expected numbers of tumors not adjusted for age or sex to match study population
Burch et al., 1987	Case–control	All brain tumors in Toronto and southern Ontario diagnosed in 1977–1981 and still resident in 1979–1982; of 328 eligible, 247 (75%) participated; comparator, matched hospital controls; of 410 controls asked to participate, 228 (56%) interviewed	Accidents, injuries that involved head (not further specified)	Brain tumors	215 matched pairs analyzed; more cases than controls reported injuries involving head (RR, 2.51; $p \leq 0.0001$), but difference not significant if head injury required medical attention (RR, 1.2; $p = 0.65$)	Matching on basis of sex, area of residence, marital status, ±5 years of birth, date of diagnosis, date of death (if death occurred)	Excluded spongioblastomas, ependymomas, meningiomas, neuroepitheliomas, pituitary adenomas, neurilemmomas. Recall bias, nonparticipation bias noted by authors
Carpenter et al., 1987	Nested case–control	Workers at two nuclear facilities in Oak Ridge, TN, in 1943–1977; cases determined by death certificate; four controls per case	Head injury, self-reported on occupational-medicine pre-employment assessments	Fatal primary malignancy of brain	82 primary brain malignancies: OR, 0.9 (95% CI, 0.2–4.2); for tumors of glial origin: OR, 1.4 (95% CI, 0.3–7.2)	Matched by race, sex, work site, year of birth, year of hire	Misclassification of exposures Outcome assessed by death certificate, excluding those who had not died of primary brain malignancy

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Reference	Study Design	Population	Type of TBI	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
Hochberg et al., 1984	Case–control	Cases with glioblastomas from three Boston, one Providence, one Baltimore hospitals; ≥15 years old; 160 of 231 (69%) of eligibles participated; 125 friend controls matched by 5-year age group	Severe: resulted in skull fracture or concussion, followed by complications (such as coma, intracranial hemorrhage, epilepsy, shock, or long-lasting impairment of memory, hearing, or vision; mild: well-described concussion or brief LOC without other complications	Glioblasatoma, histologically confirmed	Unmatched analysis on 160 cases and 128 controls: overall RR, 2.1 (95% CI, 1.1–4.0); severe RR, 3.8 (95% CI, 1.3–11.0); mild RR, 1.5 (95% CI, 0.7–3.3) Risk increased with age: RR, 10.6 (95% CI, 2.1–53.3) for ≥15 years old at time of TBI	Stratification by age; RR adjusted (unknown for what)	Participation bias, recall bias
Hu et al., 1998	Case–control	Cases fromsix major hospitals in Heilongjiang Province, China, in 1989–1995; controls from same hospitals with nonneurologic and nonneoplastic disease	History of head trauma by self-report	Histologically confirmed primary gliomas requiring surgery	34 of 218 cases vs 10 of 416 controls reported head trauma; adjusted OR, 4.85 (95% CI, 2.52–9.44)	Matching on age (±5 years), sex, area of residence	Alcohol and skull x rays also found as risk factors
Inskip et al., 1998	Double cohort; Danish population with TBI compared with Danish population	All Danish residents hospitalized with TBI, 1977–1992 (N = 228,955); comparator, Danish population without history of TBI	Concussion, fractured skull, or other head injury	Intracranial tumors of CNS	Overall SIR, 1.36 (95% CI, 1.20–1.53); ≥1 year PT SIR, 1.15 (95% CI, 0.99–1.32); no difference by cell type	None	

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Reference	Study Design	Population	Type of TBI	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
	without TBI						
Monteiro et al., 2006	Hospital-based case–control	231 patients 30–65 years old newly diagnosed with primary brain tumors in 1999–2002, admitted into 10 hospitals in Rio de Janeiro, Brazil; 261 controls matched by age, sex, region of residence from inpatients for conditions other than brain cancer	Head injury >1year before diagnosis of brain neoplasm (cases) or hospitalization (controls) by self-report; hospitalization, amnesia, LOC used as indicators of trauma severity	New diagnosis of primary brain neoplasm, including cerebral meningiomas, brain cancer, cranial nerve tumors, benign and unspecified brain tumors	Association with prior head injury: adjusted OR, 1.49 (95% CI, 1.03–2.15) By histologic type: glioma (n = 31), OR, 1.30 (95% CI, 0.71–2.35); meningioma (n = 38), OR, 1.63 (95% CI, 0.96–2.75); other with histopathology (n = 15),OR, 1.07 (95% CI, 0.52–2.21); other without histopathology (n = 23), OR, 1.92 (95% CI, 0.99–3.73) As function of severity: hospitalized (n = 15), OR, 0.78 (95% CI, 0.37–1.64); lost consciousness (n = 22), OR, 1.03 (95% CI, 0.55–1.94); amnesia (n = 5), OR, 1.48 (95% CI, 0.38–5.83); any of these (n = 31), OR, 0.93 (95% CI, 0.54–1.60) As function of number of head injuries: 1 (n = 74), OR, 1.29 (95% CI, 0.85–1.96); >1 (n = 28), OR, 3.14 (95% CI, 1.50–6.61; (p trend = 0.004) As function of years since head injury: 1–9 (n = 19),	Age, sex, education, epilepsy, alcohol consumption	Only 80% of cases confirmed histopathologically, but nonhistopathologic findings most suggestive; participation rate 94% for cases and 90% for controls; reason for hospitalization for 37.4% of controls was trauma; recall bias cannot be ruled out; information on head injury based on self-reports

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Reference	Study Design	Population	Type of TBI	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
					OR, 1.18 (95% CI, 0.73–1.89); 10–19 (n = 27), OR, 1.31 (95% CI, 1.06–1.64); 20–29 (n = 23), OR, 1.07 (95% CI, 0.91–1.27); 30–39 (n = 20), OR, 1.09 (95% CI, 0.94–1.26); ≥40 (n = 18), OR, 1.09 (95% CI, 0.96–1.24)		
Nygren et al., 2001	Retrospec-tive population-based cohort	311,006 patients hospitalized for TBI in 1965–1994 from Swedish Inpatient Register (of discharges) without current cancer vs age-, sex- and year-specific incidence rates for Swedish population	Skull trauma that survived hospitalization (ICD-7 801, 853–855; ICD-8 801, 850–854; ICD-9 801, 850–854); considered in three severity groups: concussion, severe without neurosurgery, severe with neurosurgery	Primary brain tumors occurring >1year after trauma through 1995 found by linkage with Swedish Cancer Register, Cause of Death Register, Emigration Register	281 cases of brain tumors (55 meningiomas, 161 primary brain tumors, 65 others) observed in TBI subjects (SIR, 1.0; 95% CI, 0.9–1.2); no relationship for individual types of brain tumor or severity Suggestion of increase in group 30–44 years old at time of TBI: overall, SIR, 1.3 (95% CI, 1.0–1.7); benign meningiomas, SIR, 1.0 (95% CI, 0.5–1.8); primary brain tumors, SIR, 1.4 (95% CI, 1.0–1.8); other, SIR, 1.7 (95% CI, 0.8–3.2) No suggestion of trend with time since trauma (p = 0.69) or increasing age (p = 0.25)	Stratification by age at injury, sex, years after trauma, severity of injury	Record-linkage design permits assembly of large sample, but limited information available on other risk factors; radiation only likely confounder for brain tumors, but no apparent problem in these negative findings; design adopted because of question of reliability of exposure recall in case–control studies of brain-tumor patients; completeness of ascertainment of meningiomas in registry of malignant diagnoses unknown
Phillips et	Population-	200 cases newly	History of head	Newly	99 cases, 142 controls with	Age at diagnosis,	Participation 84%

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Reference	Study Design	Population	Type of TBI	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
al., 2002	based case–control	diagnosed in January 1995–June 1998, ≥18 years old, histologic confirmation by Cancer Surveillance System at Fred Hutchinson; 400 controls, two per case matched on age ± 5 years, sex by RDD or Medicare eligibility lists; all English-speaking residents of three counties in western Washington state with telephone	trauma by self-report; considered "serious" if LOC, went to ED, or hospitalized	diagnosed meningiomas (intracranial); exposures before diagnosis (case applied to two controls) gathered by in-person interviews	any head trauma: OR, 1.83 (95% CI, 1.28–2.62); mild, OR, 3.23 (95% CI, 1.82–5.71); severe, OR, 1.27 (95% CI, 0.82–1.98); single, OR, 1.51 (95% CI, 0.99–2.29); multiple, OR, 2.75 (95% CI, 1.48–5.08) Time before diagnosis: <10 years, OR, 1.39 (95% CI, 0.72–2.68;) 10–19 years, OR, 4.33 (95% CI, 1.28–2.62); ≥20 years, OR, 1.59 (95% CI, 1.09–2.31)	sex, skull radiography, CT scanning of head; race, education left out of model when shown to have had no effect	in cases, 55% random-digit dialing controls, 67% in Medicare controls Lack of blinding of interviewers to case or control status might increase potential for recall bias Cases arising less than 1 year after trauma not excluded, so tumor might have been cause of injuries or found incidentally during workup for TBI Conditional logistic analysis with information on medical, dental exposures to radiation Dose–response relationship for number of head traumas but not expected direction with "severity" of

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Reference	Study Design	Population	Type of TBI	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
							head injury (as defined)
Preston-Martin et al., 1980	Case–control	Cases, women ≤65 years old with intracranial meningiomas identified through cancer registry living in Los Angeles County; one matched control per case from neighborhood	Head injury >2 years before interview that was medically treated by history	Meningioma, histologically confirmed	185 matched pairs analyzed: OR for head injury treated medically, 2.0 (95% CI, 1.2–3.5)	Matched by sex, race or ethnicity, year of birth (±5 years); by selecting controls from neighborhood, also matched by socioeconomic status; multivariate logistic regression	189 of 218 (87%) eligible cases interviewed; interviewers not blinded to case–control status Differential recall bias
Preston-Martin et al., 1983	Case–control	Cases, men ≤65 years old with intracranial meningiomas identified through cancer registry living in Los Angeles County; one matched control per case from neighborhood	Head injury >2 years before diagnosis by history; severe head injury defined as LOC or permanent scar	Meningiomas, histologically confirmed	105 matched pairs analyzed with exact binomial test: serious head injury not related to boxing, OR, 1.9 (p = 0.01); boxed as sport, OR, 2.0 (p = 0.03); either boxed or had severe head injury unrelated to boxing, OR, 1.8 (95% CI, 1.1–3.2)	Matched by sex, race or ethnicity, year of birth (±5 years); by selecting controls from neighborhood, also matched by SES; multivariate logistic regression	One-sided tests of significance; differential recall bias
Preston-Martin et al., 1989	Case–control	Cases, men 25–69 years old with glioma or meningioma identified through cancer registry, diagnosed in 1980–1984 in Los Angeles County;	Serious head injury >2 years before diagnosis of case that resulted in LOC, dizziness, or medical consultation	Gliomas and meningiomas, histologically confirmed	272 matched pairs (202 glioma, 70 meningiomas) analyzed with exact binomial test For history of serious head trauma ≥20 years before diagnosis: glioma, OR 0.8 (95% CI, 0.5–1.3);	Matched by sex, race or ethnicity, year of birth (±5 years); by selecting controls from neighborhood, also matched by SES;	277 of 478 (58%) eligible cases interviewed; differential recall bias less likely with different findings for meningioma and glioma

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Reference	Study Design	Population	Type of TBI	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
		one matched neighborhood control per case			meningioma, OR 2.1 (95% CI, 1.1–5.4) For meningiomas only, number of serious head injuries, p for trend = 0.01	multivariate logistic regression	
Preston-Martin et al., 1998	Case–control	Cases from eight centers in six countries (Adelaide, Melbourne, Australia; Grenoble, France; Heidelberg, Germany; Toronto, Winnipeg, Canada; Stockholm, Sweden; Los Angeles, US; men, women ≥20 years old with diagnosed glioma or meningioma	Medically treated head injuries; subgroup of serious TBI: medically treated injuries that resulted in LOC, PTA, or hospitalization; also recorded participation in sports (differed by region) that could result in TBI; proxy respondents could be used if case or control unavailable	Gliomas and meningiomas	297 gliomas, 59 meningiomas Glioma: any TBI, males, OR, 1.18 (95% CI, 0.94–1.48), females, OR, 1.03 (95% CI, 0.42–2.55); any serious TBI, males, OR, 1.13 (95% CI, 0.87–1.48), females, OR, 1.07 (95% CI, 0.74–1.56) Meningioma: any TBI, males, OR, 1.49 (95% CI, 0.86–2.57), females, OR, 0.83 (95% CI, 0.54–1.28); any serious TBI, males, OR, 1.15 (95% CI, 0.57–2.34), females, OR, 0.79 (95% CI, 0.45–1.39) Borderline increase in risk for >1 TBI in men with glioma (OR, 1.52; 95% CI, .00–2.32) but not seen in women or men with meningioma No correlation with sports	Individual and frequency matching by age and sex; some centers matched on race or geographic region; ORs computed by maximal-likelihood estimates by using both conditional, unconditional logistic regression	Subject to recall bias; different methods used for matching at different centers

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Reference	Study Design	Population	Type of TBI	Health Outcomes or Outcome Measures	Results	Adjustments	Comments or Limitations
					participation Risk of meningioma in men higher 15-24 years after trauma (OR, 5.35; 95% CI, 1.72–16.62)		
Schlehofer et al., 1992.	Population-based case–control	226 cases in Rhein-Neckar-Odenwald area of Germany with primary brain tumors diagnosed 1987–1988; controls, 418 randomly selected from residential registers	Self-reported history of head injury requiring medical attention; obtained by interview	Primary brain tumors (ICD-9 191, 191.1, 192.0), restricted to gliomas (115), meningiomas (81), acoustic neuromas (30)	For all tumor types: 46 of 226 (20%) vs 113 of 418 (27%); RR, 0.71 (95% CI, 0.5–1.1) For gliomas: 27 cases vs 66 controls; RR, 0.70 (95% CI, 0.4–1.2) For meningiomas: 13 cases vs 39 controls; RR, 0.52 (95% CI, 0.3–1.0)	Age-, sex-matching for controls	418 of 521 (72%) potential controls participated; self-reports of head trauma; no comparisons by severity or number of injuries

NOTE: CI = confidence interval, CNS = central nervous system, CT = computed tomography, ED = emergency department, ICD = International Classification of Diseases, LOC = loss of consciousness, OR = odds ratio, PT = posttrauma, PTA = posttraumatic amnesia, RDD = random-digit dialing, RR = relative risk, SES = socioeconomic status, SIR = standardized incidence ratio, TBI = traumatic brain injury.

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CONCLUSIONS AND RECOMMENDATIONS

The committee was established to evaluate and summarize the peer-reviewed literature addressing the long-term health outcomes of traumatic brain injury (TBI). The previous chapters detailed the numerous health effects that are associated with penetrating TBI and mild, moderate, and severe closed TBI. This chapter summarizes what the literature tells us about the long-term outcomes in veterans and other populations. The committee also provides its recommendations for consideration by the Department of Defense (DOD) and the Department of Veterans Affairs (VA).

QUALITY OF THE STUDIES

The clinical literature on brain injury and its treatment is quite large, however, population-based studies of TBI are few, and the methods they have used are not uniform. One problem that arises in comparing findings of studies is the definitions or criteria used for classifying the severity of brain injury. Misclassification of the severity of brain injury can occur because it often depends on negative rather than positive clinical criteria.

A variety of problems are associated with longitudinal or prospective studies of TBI. Some of the most common are the selection of only some types of patients to follow at discharge from a primary-care facility, inclusion of only patients who have survived for a particular period, inconsistent followup periods for patients in a given study group, and failure to account for the disparate person-time calculation of outcome rates. Loss to followup can also be a serious problem and is common in all longitudinal studies, especially when they involve patients with less serious injuries. Even with the most aggressive attempts to track patients, there will be losses; but not comparing those lost with those followed can leave the validity of findings open to speculation.

Many of the US studies are cross-sectional, and this limits the opportunity to learn about symptom duration and chronicity, latency of onset, and prognosis and makes it difficult to interpret the results of findings, particularly when several well-conducted studies produce inconsistent results. Furthermore, many studies rely on self-reports rather than objective measures of symptoms and exposure.

The studies of TBI patients are thus of varied quality, and it was difficult for the committee to determine outcomes across the severity levels of TBI. Although the studies have provided valuable information, many of them have limitations that hinder accurate assessment,

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including the lack of representativeness, low participation rates, and self-reporting of TBI exposure and outcomes. Some studies have inappropriate control groups or no control groups, and the definition of mild, moderate, and severe TBI differs from study to study, particularly in the moderate category.

OVERVIEW OF HEALTH OUTCOMES

It is clear that sustaining TBI can have detrimental effects on a person, whether the injury is mild, moderate, or severe. The committee found many instances of long-term outcomes that are associated with TBI; some acute outcomes resolved or lessened over time (such as some neurocognitive and psychosocial findings), and other sequelae became more apparent several years after injury (such as psychiatric conditions). Many studies found a dose–response relationship with regard to TBI severity and outcome: generally, the more severe the TBI, the more severe the outcome. For example, with regard to neurocognitive outcomes, the committee found sufficient evidence of an association between penetrating TBI and decline in neurocognitive function associated with the region of the brain affected and the volume of brain tissue lost. The evidence was consistent in veterans of World War II and Vietnam. With regard to closed head injuries, the committee found sufficient evidence of an association between severe TBI and neurocognitive deficits, limited but suggestive evidence of an association between moderate TBI and neurocognitive deficits, and inadequate and insufficient evidence of an association between mild TBI and neurocognitive deficits.

With regard to neurologic effects, the studies reviewed had numerous findings, including a strong association between TBI and unprovoked seizures. For example, there is a causal association between penetrating TBI or severe closed TBI and unprovoked seizures, whereas the evidence of risk of unprovoked seizures after mild TBI is limited and suggestive of an association. In general, the risk of seizure after all levels of TBI severity appears to be highest in the first year after trauma and to decline thereafter. Some of the literature reviewed supports an association between TBI and neurodegenerative diseases, for example, studies that yielded sufficient evidence of an association between moderate or severe TBI and dementia of the Alzheimer type or parkinsonism, although an association with dementia pugilistica could be supported only in professional boxers. Other studies reviewed did not support a relationship between TBI and multiple sclerosis or amyotrophic lateral sclerosis and were categorized as inadequate and insufficient to determine whether an association exists. There were endocrine outcomes, such as sufficient evidence of an association between moderate to severe TBI and growth hormone insufficiency and hypopituitarism, however, the studies only supported a finding of limited and suggestive evidence of an association between moderate to severe TBI and diabetes insipidus.

Psychiatric outcomes have been discussed by the committee, and there is some uncertainty regarding the mechanisms linking TBI and psychiatric diagnoses. For example, it is not clear whether psychopathologic conditions after TBI are biologic consequences of the injury, a reaction to the person's cognitive and social dysfunction after TBI, or a continuation of pre-existing conditions. The committee has chosen to use the terminology of primary psychiatric disorders, as has been the custom in the TBI literature. The committee notes that the predominance of studies indicated that groups with TBI (mild, moderate, or severe) had higher rates of major depression 6 months or more after TBI than did appropriate comparison groups.

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The committee concluded that there is sufficient evidence of an association between TBI and depression and aggressive behaviors. The association between mild TBI and posttraumatic stress disorder appears to be different between military and civilian populations. Studies of military personnel who served in the Gulf War led the committee to conclude that there is limited but suggestive evidence of an association between TBI and PTSD. In contrast, studies of civilian populations led the committee to conclude that there is inadequate and insufficient evidence to determine whether an association between TBI and PTSD exists. The studies yielded sufficient evidence of an association between TBI and aggressive behaviors, but limited but suggestive evidence of an association between TBI and decreased alcohol and drug use. Finally, the studies yielded limited but suggestive evidence of an association between moderate to severe TBI and psychoses generally appearing in the second and third years after TBI.

Social functioning is often severely hampered after TBI. Social function in those hospitalized with TBI is adversely affected, relative to those with no injury, for at least 1 year. Results of some studies suggest that difficulties might continue up to 15 years after injury, depending on TBI severity. TBI decreases the probability of postinjury employment in people who were employed before they were injured, lengthens the time it takes them to return to work (if they do return), and decreases the likelihood that they will return to the same positions. Those adverse effects are related to the severity of injury as measured with neurologic severity indicators and are related even more strongly to post-TBI neuropsychologic impairment. Penetrating head injury sustained in wartime clearly is associated with unemployment. The probability of being employed 15 years after the Vietnam War was related to the number of residual neurologic deficits, brain-volume loss, and cognitive status. TBI also adversely affects leisure and recreation, social relationships, functional status, quality of life, and independent living. By 1 year after injury, psychosocial problems appear to be greater than problems in basic activities of daily living. The committee concluded that there was sufficient evidence of an association between penetrating TBI and long-term unemployment and between moderate to severe TBI and long-term adverse social-function outcomes, particularly unemployment and diminished social relationships. However, the committee concluded that there was inadequate and insufficient evidence of an association between mild TBI and long-term adverse social functioning, including unemployment, diminished social relationships, and decrease in the ability to live independently.

There is sufficient evidence of a causal relationship between injury and premature death in people who survive penetrating head injury. There is inadequate and insufficient evidence to determine whether an association exists between mild, moderate, and severe TBI and premature death in people who survive TBI for 6 months or longer; that is largely because of the paucity of studies. Finally, in the subset of patients with moderate or severe TBI either admitted into or discharged from rehabilitation centers or those receiving disability support, there is sufficient evidence of an association between TBI and premature death; however, this finding is limited to patients who have sustained injuries severe enough to warrant inpatient rehabilitation or disability support.

Large population-based registry studies of brain cancer found no association between TBI and brain tumors. However, there is evidence from some other studies of a weak but significant association between TBI and meningioma and of an increase in risk of brain tumors 10 years or more after TBI; this suggests a long latent period before clinical presentation. The committee believes that the possibility of an association between TBI and brain tumors is not a

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closed question and that longer-term followup, especially in large registry-based studies, is warranted to determine whether there is a measurable increase in risk and, if so, when it is most likely to be observed. For now, the committee concludes that the inconsistent results among the studies are most supportive of a classification of inadequate and insufficient evidence to determine whether an association exists.

RECOMMENDATIONS

Scoring of Severity of Blast Induced Neurotrauma

BINT is a complex type of TBI that features closed (blunt) head injury that may be accompanied by a penetrating brain injury. The pathobiology of BINT parallels that of TBI. Because moderate, moderate to severe, and severe blast-induced neurotrauma (BINT) is often part of complex polytrauma, proper diagnosis of BINT should include both classification of blast injuries and scoring of the severity of head injury. The most recent version of the AIS incorporates blast injuries and is regularly used by the US Army; it can be used for global scoring of all injuries. In hospitals, the modified Pathology Scoring System can yield additional information that might be valuable in designing treatment strategies and predicting outcomes. A combination of the head AIS, as an anatomic measure, and the GCS, as a physiologic measure of brain-injury severity, is useful in initial estimation of brain damage. Nevertheless, use of additional TBI scoring systems is recommended, especially in the case of mild TBI or suspected concussion or when medical records provide less detailed information about the injury and its circumstances. In the military environment, use of the Brief Traumatic Brain Injury Screen and the Military Acute Concussion Evaluation is recommended for every soldier who has a history of blast exposure (even low-intensity blast exposure).

The committee recommends that the Department of Defense use the Brief Traumatic Brain Injury Screen and the Military Acute Concussion Evaluation for every soldier who has a history of blast exposure (even of low-intensity blast exposure).

Experimental and Clinical Studies of Blast Induced Neurotrauma

Blast injury, especially BINT, is a continuing threat to our troops. In both civilian and military environments, exposure to a blast might cause instant death, injuries with immediate manifestation of symptoms, or injuries with delayed manifestation. There is a paucity of information in the scientific literature regarding the sequelae of blast injury, and there is a need for prospective, longitudinal studies to confirm reports of long-term effects of exposure to blasts. Because of lack of information, adverse neurologic and behavioral changes in blast victims might be underestimated, and valuable time for preventive therapy or timely rehabilitation might be lost.

The committee recommends that the Department of Defense and the Department of Veterans Affairs support prospective, longitudinal studies to confirm reports of long-term or latent effects of exposure to blasts. Those studies should examine the consequences of blast-induced neurotrauma, recovery timeline, and any factors that improve or worsen outcomes.

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Additionally, animal models provide the framework for predicting outcomes and developing optimal therapeutics for BINT; however, after reviewing the literature, the committee came to the conclusion that there is a need for more refined animal models of BINT. They should be aligned with emerging data on the human response to BINT. The accessibility to acute clinical data on human BINT from DOD and VA is essential for refining the animal models.

The committee recommends that the Department of Defense and the Department of Veterans Affairs support research on animal models of blast-induced neurotrauma. Consideration should be given to developing models that would be relevant to human traumatic brain injury that encompass a more comprehensive experimental design. That could include studies that measure both behavior and pathology that might differ with traumatic brain injury severity. It would be important for the Department of Defense and the Department of Veterans Affairs to work with the research community and provide acute clinical data on human blast-induced neurotrauma to enable refinement of the animal models.

Registry Control Groups

The studies of TBI evaluated by the committee had numerous limitations. A primary limitation results from the nature of the control or comparison group assembled by the investigator. In an attempt to improve the quality of future TBI studies, the committee has described what it considers to be appropriate control groups.

Evaluating whether TBI in service members is associated with particular outcomes requires comparison groups of service members who have experienced injuries other than TBI and service members who have been deployed but not injured. Comparing outcomes of TBI with outcomes in those reference groups is the only means of identifying which outcomes are due solely to TBI and not to deployment or to injury in general.

The committee recommends that the Department of Veterans Affairs include, in the development of the Traumatic Brain Injury Veterans Health Registry (hereafter referred to as "the registry"), other service members who could provide a valid comparison for the analysis of outcomes. Comparison groups should be made up of injured persons without traumatic brain injury or blast exposure, uninjured deployed veterans, and uninjured nondeployed but previously active-duty veterans. Those groups could be compared with persons who have received a diagnosis of traumatic brain injury and with those who have possible or probable traumatic brain injury. The three comparison groups should have samples large enough to provide reference rates of outcomes of interest. Furthermore, the registry needs to be representative of the traumatic brain injury population to be able to determine associations between such injury and various outcomes. There should be no exclusions on the basis of sex, race, geographic region, or rank.

Access to medical records is essential to ensure the validity of a recommended research design. Neurologic status, computed tomographic or magnetic resonance imaging, electroencephalography, associated nonbrain injuries, and durations of impaired consciousness and PTA amnesia are important for the accurate classification of service members into appropriate groups.

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For the registry to have the greatest benefit, predeployment information on all groups mentioned above should be made available to the injury-research community. Complete medical information on outcomes of each person (stripped of personal identifiers) in the registry should be available whether or not care is sought at or covered by the VA system.

Predeployment and Postdeployment Testing

In considering the question of long-term outcomes of TBI, questions arise that are very seldom addressable in current studies: What was the predeployment cognitive ability of the person? How did the TBI affect the baseline functioning? The answers to those questions are important in isolating and understanding the effects of TBI itself on long-term outcome. Most information about TBI effects comes from studies of World War I, World War II, and Vietnam veterans, but those studies are based on penetrating or severe closed head injuries. In the current conflict, many injuries are related to blast, and outcomes are unknown.

In an effort to understand the long-term outcomes of traumatic brain injury, including consequences that might be related to blast, the committee recommends that *all* deployed military personnel undergo predeployment neurocognitive testing. The committee also recommends postdeployment neurocognitive testing of representative samples of military personnel (including those with traumatic brain injury, those with other non-TBI injuries, and uninjured service members without blast exposure).

Among service members with predeployment and postdeployment testing, it should be possible to link the results for each person with DOD and VA records, and those should be made available for research and treatment.

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