Mild Head Injury

Relation to Cognition, Dementia, Fatigue & Genetics

~ *Anna Sundström* ~

ABSTRACT

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Following a mild head injury (MHI), a person may report a variety of symptoms such as headache, memory disturbance, dizziness, and concentration difficulties. For most persons the symptoms are transient, but some suffer persistent symptoms that can have a major impact on everyday life. It remains poorly understood why some but not others have full recovery after MHI. The aim of this thesis was to investigate outcomes after MHI, with particular focus on neuropsychological functioning, fatigue, and risk of dementia. A related objective was to examine the potential association of a genetic factor, *Apolipoprotein* (*APOE*), with MHI outcome. The *APOE* ε4 allele has been associated with unfavorable outcomes after moderate or severe head injury, but little is known about its influence on outcome after MHI. In Study I and II, data from a population-based longitudinal study were used to compare neuropsychological functioning and fatigue before and after MHI. The results from Study I showed a post-injury decline in neuropsychological performance for ε4-carriers, whereas the performance remained unchanged for non-carriers. Study II showed an increase in self-reported fatigue after MHI for both ε4-carriers and non-carriers, with a more pronounced increase for ε4-carriers. In Study III, a case-control study was conducted to examine whether a history of MHI increased the risk of developing dementia later in life. It was found that MHI alone did not increase the risk, but the combination of MHI and *APOE* ε4 was associated with increased risk of dementia. Taken together, the studies generally indicate a positive outcome after MHI, but in combination with *APOE* ε4 even mild head injury may lead to long-lasting negative outcomes. Consideration of pre-injury level of functioning and genetic factors seems critical for a complete understanding of the impact of MHI.

Key words: Mild head injury, mild brain injury, concussion, neuropsychology, fatigue, dementia, preinjury, postinjury, within-subject, apolipoprotein, APOE.

PREFACE

This doctoral dissertation is based on the following articles, which will be referred to in the text by their Roman numerals:

I   Sundström, A., Marklund, P., Nilsson, L-G., Cruts, M., Adolfsson, R., Van Broeckhoven, C., & Nyberg, L. (2004). *APOE* influences on neuropsychological function after mild head injury: Within-person comparisons. *Neurology, 62,* 1963-1966.

II   Sundström, A., Nilsson, L-G., Cruts, M., Adolfsson, R., Van Broeckhoven, C., & Nyberg, L. (2006). *Fatigue before and after mild head injury: pre-post injury comparisons in relation to Apolipoprotein E.* Department of Psychology, Umeå University, Sweden. Manuscript submitted for publication.

III   Sundström, A., Nilsson, L-G., Cruts, M., Adolfsson, R., Van Broeckhoven, C., & Nyberg, L. (2006). *International Psychogeriatrics, May 10*; 1-7. [Epub ahead of print]

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CONTENTS

INTRODUCTION

Mild head injury (MHI) is something that many suffer—as a result of accidents, from sports activity, or in a myriad of ways. A MHI can lead to a brief loss of consciousness or cause the person to feel dazed and/or confused. Most individuals who suffer a MHI return to their usual daily activities within a few days or weeks (Dikmen et al., 1986; Gentilini et al., 1985; Levin et al., 1987). However, for some individuals, MHI has a much less benign course. A significant percentage of individuals experience long-lasting symptoms, impairment, and disability such as impaired memory, concentration difficulties, headache, and fatigue. These problems can significantly alter individuals´ everyday life, MHI may even increase their long-term risk of developing Alzheimer's disease or other dementia disorders (Bennett & Raymon, 1997; Goldstein, 1990; Gronwall & Wrightson, 1974; Rimel et al., 1981).

Why some individuals exhibit long-term symptoms is a matter of continuing debate, especially since imaging scans usually cannot detect objective evidence of brain injury. Research on MHI has been inconsistent, a result that might partly be explained by methodological issues (Bernstein, 1999), such as lack of controls and lack of a generally accepted definition of MHI (Dikmen & Levin, 1993). Another source of bias, highlighted by McCullagh & Feinstein (2003), involves discrepancies in subject participation, especially in longitudinal studies of MHI. McCullagh & Feinstein showed that those who agree to participate in a prospective study on outcome after MHI have more severe injuries (longer loss of consciousness, increased post-traumatic amnesia duration, and positive brain-imaging scan) than those who decline to participate. In addition, they suggested that the common use of the in-patient population in most studies might have led to an overestimation of the magnitude of poor outcome after MHI.

At a more microscopic level, a specific gene, Apolipoprotein E (*APOE*), has been hypothesized to influence the brain's susceptibility and response to head injury. The *APOE*, a polymorphic gene, has three primary alleles. One of these (allele ε4) has been associated with less favorable outcomes after head injury (Jordan et al., 1997; Teasdale et al., 1997). In 1995, Mayeux et al. demonstrated that individuals with no history of head injury had a ten-fold increased risk of Alzheimer's disease if they had the ε4 allele gene compared to individuals without the ε4 allele. Since this study, several studies have been conducted in humans and in animals; however, the

results have been inconclusive. Whereas studies on animals have revealed clear links between the ε4 allele and outcomes after head injury, studies on humans have produced mixed results (Nathoo et al., 2003a). Clearly, more studies are needed that investigate MHI and its association with the *APOE* gene.

This thesis uses data from the Betula project, a longitudinal population-based study, to examine outcomes after MHI by focusing on the influence of the *APOE* ε4 allele on neuropsychological performance, fatigue, and risk for dementia. The longitudinal design provided us access to both pre- and post-injury data, making within-person comparisons possible. The thesis will start with a review of the relevant background literature.

The term *mild head injury* (MHI) is often used interchangeably with *mild brain injury, mild traumatic head injury, mild traumatic brain injury, minor head injury, minor brain injury,* or *concussion* (King, 1997). Due to lack of agreement with respect to the meaning of these terms, Rosenthal (1999) recommend using 'mild head injury' or 'mild head trauma' because these terms do not imply that an actual injury to the brain has occurred, at least not to the same degree that 'brain injury' does. Consequently, the term 'mild head injury' (MHI) will be used throughout this thesis.

GENERAL BACKGROUND

Definition of mild head injury

A MHI can range from a minor bump to the head that makes someone feel 'dazed' for a few seconds, without any need for treatment, to a significant period of unconsciousness requiring hospitalization, associated with visible abnormalities on CT-scans. There is no uniformly accepted definition of MHI. In addition, comparisons regarding outcome and the prevalence of long-lasting sequelae are difficult when different criteria for inclusion and exclusion are used (Dikmen & Levin, 1993). In 1993, the *Mild Traumatic Brain Injury Committee* (MTBIC) of the *American Congress of Rehabilitation Medicine* (ACRM) delineated inclusion criteria for MHI, criteria that are the perhaps most used today. These criteria will be used throughout the remainder of this thesis and are outlined in Table 1.

Table 1.
Definition of mild head injury developed by the Mild Traumatic Brain Injury Committee of the American Congress of Rehabilitation (1993)

Definition:
A person with mild traumatic brain injury is a person who has had a traumatically-induced physiological disruption of brain function. Such injury is manifested by at least one of the following:
1. any period of loss of consciousness;
2. any loss of memory for events immediately before or after the   accident;
3. any alteration in mental state at the time of the accident (e.g., feeling dazed, disoriented, or confused); and
4. focal neurological deficit(s) that may or may not be transient.
But where the severity of the injury does not exceed the following:
posttraumatic amnesia (PTA) not greater than 24 hours
after 30 minutes, an initial Glasgow Coma Scale (GCS) of 13-15
loss of consciousness of approximately 30 minutes or less
Causes of traumatic brain injury:
a) the head being struck, and/or,
b) the head striking an object, and/or
c) the brain undergoing movement in the skull without any direct external trauma to the head.
This definition excludes stroke, anoxia, tumor, encephalitis, etc.

Incidence and causes of mild head injury

MHI is common. It has been estimated that 80% (Miller, 1993; van der Naalt, 2001) to 95% (Vos et al*.,* 2002) of all head injuries experienced in Europe can be considered as mild. In their overview of the incidence of MHI, Cassidy et al. (2004) estimated that the incidence of MHI among hospital-treated adults was between 100 and 300 per 100,000. However, since the majority of MHI are not documented in emergency or medical departments, these figures likely underestimate the true incidence of MHI, and a more plausible estimate probably exceeds 600/100,000 (Cassidy et al., 2004; Dacey & Dikmen, 1987). In Sweden, estimates of the incidence for MHI range from 191/100,000 (Britton et al., 2000) to 718/100,000 (Bring et al., 1996).

The number as well as the cause of MHI varies largely between different countries due to, among other things, differences in numbers of motor vehicles, traffic safety regulations, road transport infrastructure, alcohol and drug policy, driver licensing, speed limits, safety laws (e.g., seat belt laws), work related safety factors, and socioeconomic factors. The majority of causes of MHI, however, are generally motor vehicles, incidents and falls, assaults, and sport injuries comprising the bulk of the remainder proportion (Cassidy et al., 2004). In Sweden, accident data shows that 50-60% of MHI individuals admitted to a hospital received their injury in a fall and 25% received their injury while operating a motor vehicle (Peloso et al., 2004). Males have more than twice the rate of MHI than women, with the exception of the age group 75 years and older. Males between 15 and 24 years have the greatest number of MHI. Some have suggested that this overall gender difference is due to increased risk-taking behavior and greater alcohol consumption among men, in particular in those between the ages of 15 and 24 years (Binder, 1987; Kraus, 1993).

Other suggested risk factors for sustaining a MHI are low socioeconomic status, unemployment, low education, alcoholism (accounting for approximately 18% of cases), prior head injuries (8%), or other central nervous system disorders (3%) (see Lezak, 1995).

Biomechanics of mild head injury

Head injuries are generally categorized as primary (direct) injuries and secondary (indirect) injuries depending on their time course. Primary injuries– e.g., skull fractures, contusions, and diffuse axonal contusions–are sustained at the time of impact. Indirect (secondary) injuries–e.g., brain swelling, toxic processes, blood vessel damage, and changes in blood volume and blood flow–develop over time. Increased intracranial pressure is probably the most severe secondary injury. This situation is especially dangerous to the lower brainstem structures where increased pressure often results in death (Lezak, 1995). Axonal damage has been shown to progress within the first 12 to 24 hours after injury; therefore, it may be better viewed as falling in-between primary and secondary injury (Graham et al., 2000).

Head injuries can also be categorized into open/penetrating injuries and closed head injuries, in which the skull remains intact, and as being either focal or diffuse (Gennarelli et al., 1982). It is important to note that few individuals with traumatic head injuries have only focal or only diffuse injuries (except for very mild injuries, which usually only are diffuse); in other words, focal injuries almost always exhibit some evidence of diffuse injury and vice versa (Adams et al., 1989; Gennarelli & Graham, 1998; Graham et al., 2000).

Focal injury

Focal damage can occur directly at the contact point of trauma, at the directly opposite side of the brain, or at both sides; however, they are limited to local area damage by definition. Damage at the opposite side of the brain is especially common when the primary impact to the brain is occipital; in these injuries, almost everyone sustains opposite frontal side lesions. To pinpoint the site of trauma, we need to understand the constellation of symptoms that can occur after a focal injury. Well-defined focal damage is unusual when a huge force is involved, as in motor vehicle collisions (Lezak, 1995).

Diffuse injury

Diffuse axonal damage can arise after sudden impact or acceleration/deceleration mechanisms where the forward energy is transformed into a rapid deceleration and a wave shape movement of the brain. This type of response is usually followed by rapid rotational movement. The back and forth movement of the brain inside of

the skull stretches axons and blood vessels to the point at which they may rupture, causing axonal damage. This diffuse damage generally results from motor vehicle collisions or falls (Adams et al., 1989; Blumbergs et al., 1994; Graham et al., 2000; Polvishock et al., 1983).

Classifying head injury severity

MHI may be classified in several ways. Unfortunately, no consensus exists over which factors are most important and which criteria are best used to classify MHI. There are, however, several points of agreement that concern the use of one or more generally accepted assessment tools–including the *Glasgow Coma Scale* (GCS)–as well as assessments for post-traumatic amnesia (PTA), level of consciousness (LOC), and the use of different neuroimaging techniques (WCB, 2003).

Clinical severity is usually based on assessments performed soon after an injury (Alexander, 1995). Based upon these assessments, head injury is usually graded as mild, moderate, or severe (Teasdale & Jennett, 1974).

The Glasgow Coma Scale

The *Glasgow Coma Scale* (GCS) was initially developed to measure the depth of coma (Teasdale & Jennett, 1974), and is a somewhat crude measure. Nonetheless, it is now one of the most widely-used tools, both to assess head injury severity and to predict clinical outcome. The GCS assesses a patient's response to simple stimuli, including their best motor response, best verbal response, and degree of eye opening. To assign the GCS score, the results from these three scores are combined. Head injuries associated with a GCS score of 13 to 15 are generally classified as mild, 9 to 12 as moderate, and 8 or less as severe (see Table 2).

When assessing the severity of a coma using the GCS, it is crucial to consider the effects of alcohol, medications, or drug intoxication, effects that can deepen a coma, leading to a lower GCS score (Dikmen & Levin, 1993). As stated earlier, another thing to consider is the time between the injury and the first GCS assessment. (Since GCS seldom can be assessed immediately, there is almost invariably a time lag). Nevertheless, GCS assessment should be conducted as soon as medical professionals arrive. The time when the GCS is used for assessment relative to the injury should be recorded. This is especially important when considering MHI

since these patients often improve considerably within the first few hours after injury. Moreover, the GCS score cannot be determined retrospectively (Ruff & Jurica, 1999).

The GCS has good inter-rater reliability (r=.95), test-retest reliability (Spearman´s rho=.85), and construct validity (Pearson's r=.68), but it is not a very good predictor of outcome (Pearson's r=.56) (Segatore & Way, 1992). Because GCS can help identify severe head injuries, it is an effective tool to use when determining treatment for patients with severe trauma (Bastos el al., 1993); however, because GCS is not sensitive enough to determine the degree of coma severity in milder cases (GCS scores between 13 and 15), it is not a valid way to predict outcomes within the heterogenic MHI group (Gomez et al., 1996; Stein et al., 1993). To address the problem of assessing milder injuries, an extended version of the Glasgow Coma Scale (GCS-E) that includes an amnesia score has been developed (Nell et al., 2000).

Table 2
The Glasgow Coma Scale (GCS)

	Score
Eyes Open	
Spontaneously	4
To Speech	3
To Pain	2
Absent	1
Verbal	
Converses/Oriented	5
Converses/Disoriented	4
Inappropriate	3
Incomprehensible	2
Absent	1
Motor	
Obeys	6
Localizes Pain	5
Withdraws (flexion)	4
Decorticate (flexion) Rigidity	3
Decerebrate (extension) Rigidity	2
Absent	1

Post-traumatic amnesia

Another widely used index of clinical severity in head injury pertains to the duration of post-traumatic amnesia (PTA). PTA can be defined as the length of time after a head injury when a patient is confused or disorientated or has undue fatigue, impaired concentration, poor attention, and/or an inability to consolidate new memories (Crovitz & Daniel, 1987; Gasquoine, 1991; Shores et al., 1986). The duration of PTA can be affected by a person's age; the elderly generally experience longer PTA. It can also be influenced by alcohol, medications and drugs, influences that can make the true estimate of PTA difficult, generally leading to an overestimation of the length of PTA (Haslam et al., 1994; Saneda & Corrigan, 1992). PTA correlates well with the GCS, but it seems to predict outcome better (Bishara et al., 1992). Another advantage of PTA is that it can be assessed both prospectively and retrospectively; however, the reliability of retrospective self-reports has been questioned (Corrigan et al., 1992). For example, Gronwall and Wrightson (1981) found that after 3 months 25% of MHI patients had altered their initial report of PTA duration.

The following is a rough guideline to assess the severity of injury and predict brain injury recovery: PTA less than 1 hour indicates a mild head injury; PTA up to 1 day indicates a moderate injury; and PTA beyond one week indicates very severe injury. McKinlay and Watkiss (1999) have developed more refined categories (see Table 3).

The first standardized test of PTA was the *Galveston Orientation and Amnesia Test* (GOAT) (Crovitz & Daniel, 1987). The GOAT is a widely used test in acute care settings and consists of 10 standardized questions that assess the recall of events before and after the injury and determines general orientation: name, day of the week, and first event remembered after the injury (Levin et al., 1979).

Table 3

Post-traumatic Amnesia Guidelines (after McKinlay and Watkiss, 1999)

PTA 1 day or less: Expect rapid and full recovery with appropriate management. A few may show persistent disability, usually '*post-concussion syndrome'*.
PTA over 1 day, but less than 1 week: The recovery period is more prolonged–now a matter of weeks or months. Full recovery is possible, for most of these cases, with good management.
PTA 1 to 2 weeks: Recovery requires several months. Many patients will be left with residual problems, even after the 'recovery' process has ended, but one can be reasonably optimistic about functional recovery (returning to employment, social activities, etc.) with good management.
PTA 2 to 4 week: The process of recovery will be very long–1 year or longer is not unusual. Permanent deficits are likely. There must be some pessimism about functional recovery when PTA reaches these lengths.
PTA over 4 weeks: Permanent deficits and, indeed, significant disability, now are virtually certain. It is not just a matter of 'recovery', but of long-term retraining and management.

Loss of consciousness

To predict severity and outcome, it is important to establish whether a patient experienced loss of consciousness (LOC) in association with a head injury. LOC can correlate with risk of cranial fracture and intracranial complications (Gomez et al., 1996; Stein & Spettell, 1995; Vos et al., 2002); however, structural damage can occur without any LOC. In addition, as was noted above, the diagnosis of MHI does not require any loss of consciousness (Abdel-Dayem et al., 1998; Varney & Varney, 1995). There exists no consensus regarding the duration of LOC relative to the various classifications of MHI severity (Vos et al., 2002). In moderate or severe injuries, length of LOC can be a gross predictor of outcome, but in a mild head injury there seems not to be any association between brief periods of LOC and clinical outcomes.

Neuroimaging techniques

A number of neuroimaging techniques are available to assess injury severity: Computed Tomography (CT) Scan, Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET), and functional MRI (fMRI) (McAllister et al., 2001; De Kruijk et al., 2001). The CT scan, the 'gold standard' for detecting intracranial hemorrhages, is the most common technique used with MHI patients. Most MHI patients have normal CT; however, 3-13% of MHI patients with a GCS score of 15 have intracranial abnormalities and 25-37.5% with GCS scores of 13 show intracranial abnormalities–1% of these patients requires neurosurgical intervention (Vos et al., 2002). Because CT scans are expensive, it is crucial to identify patients most likely to benefit from a CT scan (Glauser, 2004).

Stiell et al. (2001) developed clinical guidelines, the *Canadian CT Head Rules*, to establish when to use CT for milder injuries (i.e., to identify patients at risk for intracranial lesions). These guidelines are 98.4% (95% CI 96-99%) accurate when identifying patients at risk for developing intracranial lesions. The guidelines help identify patients with GCS scores of 13-15 and any one of the following: GCS score <15 at 2 h after injury; suspected open or depressed skull fracture; any sign of a basal skull fracture; vomiting ≥ two episodes; age ≥ 65 years; retrograde amnesia > 30 min; and injury cause by especially-dangerous mechanisms (a pedestrian struck by a motor vehicle, an occupant ejected from a motor vehicle, or a fall from a height > 3 feet or five stairs).

MRI is a more sensitive imaging technique than CT, and abnormalities (e.g., white matter shearing) that are not visible on CT scans can sometimes be seen on MRI (Mittl et al., 1994; Rugg-Gunn et al., 2001). MRI is better than CT in assessing structural causes of neurological deficits, and can be useful for persons with long-term sequelae (Vos et al., 2002). Other techniques that seem promising for examining severity of injury, but which require additional research to clarify their clinical utility, include Positron Emission Tomography (PET), functional MRI (fMRI), single photon emission computed tomography (SPECT), and various biochemical markers (Ingebrigtsen et al., 1997).

In summary, the most commonly used assessment tools, GCS and PTA, are not sensitive enough to predict outcome after MHI. CT scan can detect intracranial abnormalities, but may miss other abnormalities such as white matter sheering.

MRI and other more advanced imaging techniques are more sensitive for detecting most abnormalities.

Post-concussion syndrome

MHI can cause a cluster of symptoms (both acute and long-term) that fall into three broad categories: cognitive problems (e.g., memory deficits); physical complaints (e.g., headache, fatigue); and psychological symptoms (e.g., depression, anxiety). Generally, individuals recover from these symptoms without any residue within 1-3 months (Alexander, 1995; Dikmen et al., 1986; Gentilini et al., 1985; Levin et al., 1987; Ponsford et al., 2000). Several studies, however, report persistent symptoms months after injury (Dikmen et al., 1986; Alves et al., 1993) and even years after injury (Alexander, 1995; Bohnen & Jolles, 1992; Brown et al., 1995; Levin et al., 1987; Rutherford et al., 1978). The estimated prevalence of symptoms lasting months or longer is quite unclear: 7-8% (Binder, 1997); 10-25% (Alexander, 1995; Ponsford et al., 2000); approximately 33% (Rimel et al., 1982); and 80% (Bohnen & Jolles, 1992). When these symptoms persist, a Post Concussion Syndrome (PCS) exists.

* *Cognitive deficits*: Tasks that are most likely to show deficits are those that require fast processing, working memory and attention, declarative long-term memory, and executive functions (Alexander, 1995; Binder et al., 1997; Frencham et al., 2005). In general, these deficits are believed to resolve within 3 months (see Carroll et al., 2004). Consequently, there have been a limited number of studies that have investigated cognitive outcomes beyond 3 months despite subjective reports of longer-lasting cognitive deficits (Bohnen et al., 1995). Most studies have failed to identify long-term deficits (Goldstein et al., 2001; McAllister et al., 2002; Voller et al., 1999). Evaluating cognitive outcome beyond 3 months, two relevant meta-analyses found a small but significant effect on cognitive functioning (Binder et al., 1997; Frencham et al., 2005); however, to obtain an overall estimate of effects, the results from different tests are often pooled and different cognitive tasks are grouped according to superior cognitive domains. In the past, tasks showing low sensitivity after MHI (e.g., Digit Span) often have ended up in the same cognitive domain as tasks with high sensitivity (e.g., PASAT). There is an apparent risk that insignificant results from an insensitive task may mask significant results from a sensitive task, yielding overall false negative results (Cicerone, 1997; Frenchmen et al., 2005). Unfortunately, far too few studies exist that investigate specific tasks.

Physical symptoms: Physical symptoms include headache, fatigue, dizziness, blurred vision, light and sound sensitivity, and sleep disturbance. Fatigue is one of the most reported symptoms (Borgaro et al., 2005; Emanuelsson et al., 2003; Evens, 1992; Haboubi et al., 2001; Kashluba et al., 2004; LaChapelle et al., 1998; McCullagh et al., 2001; Paniak et al., 2002a; Ponsford et al., 2000; Stulemeijer et al., 2006; van der Naalt et al., 1999; Ziino & Ponsford, 2005, 2006). Severe fatigue may affect cognition, interfering with return to work and limiting social interactions. In addition, people with head injuries often report fatigue as their most difficult issue with respect to their quality of life (Alves et al., 1993; Dumont et al., 2004; van der Naalt et al., 1999). Shortly after a MHI, persons often report that they become fatigued easily; 29% to 47% report fatigue within the first 3 months (LaChapelle & Finlayson, 1998; Levin et al., 1987). For example, a recent study by Borgaro et al. (2005) found fatigue to be significantly more reported among MHI than among controls and to be unrelated to head injury severity, days post-injury (3-81 days), gender, and cognitive performance. Fatigue has been shown to be rather persistent over time. For example, one study of mild and moderate head injury assessed 1, 3, 6, and 12 months post-injury found fatigue to be reported by 57%, 61%, 45%, and 45% respectively (van der Naalt et al., 1999).

Although fatigue is a common symptom after a head injury, it is also reported among 5-20% of the general population and is a frequent symptom in medical conditions, such as autoimmune disease, cancer, multiple sclerosis, and diabetes.

* *Psychological symptoms:* Depression commonly occurs after MHI (Busch & Alpern, 1998; Holsinger et al., 2002). Other psychological symptoms commonly reported after head injuries are anxiety and irritability (Alexander, 1995; Bernstein, 1999; Gouvier et al., 1992; King, 1997; Levin, 1987; Rutherford et al., 1978). Because these symptoms often coexist, they can be difficult to assess. For example, physical symptoms such as fatigue and sleeping difficulties have been shown to correlate highly with depression and anxiety (van der Linden et al., 1999).

To encourage more research and communication among researchers, PCS has been included in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition. The proposed criteria (which are tentative since research is ongoing) include: (1) a history of head trauma that has caused significant cerebral concussion (e.g., with loss of consciousness, post-traumatic amnesia, or seizures); (2) neuropsychological evidence of difficulty in attention or memory; and (3) three or more symptoms that last at least 3 months and have an onset shortly after head trauma or represent

substantial worsening of previous symptoms (fatigue, disordered sleep, headache, dizziness, irritability/aggression, anxiety/depression/affect labiality, changes in personality, or apathy/lack of spontaneity). Finally, the criteria state that symptoms must result in significant impairment in daily functioning.

In the literature, however, there is still no consensus in terms of how many symptoms are needed to diagnose PCS. Not all authors agree with the definition of sequelae in PCS; instead, they suggest that PCS just consists of a cluster of co-morbid symptoms and that each symptom is caused by a different underlying mechanism (McAllister & Arciniegas, 2002). Diagnosing PCS is also difficult because virtually all the symptoms listed in the PCS criteria have a high basal rate in the general population (Dikmen & Levin, 1993; Satz et al., 1999) and these symptoms are exhibited in other conditions not involving injury to the head, including post-traumatic stress disorder (Hickling et al., 1998), anxiety/depressive disorders (King, 1997; McCauley et al., 2001), and chronic pain (Gasquoine, 2000; Smith-Seemiller et al., 2003). In addition, proper comparison groups usually have been missing in studies.

Etiology of post-concussion syndrome

The etiology of symptoms lasting beyond 3 months is controversial, and whether these symptoms are organic or psychogenic probably remains the least agreed upon question in the MHI literature (Jacobson, 1995; Lishman, 1988; Lezak, 1995). This debate has a long history. Initially, the belief was that symptoms, almost exclusively, were secondary to psychological factors, often resulting from neurotic personalities or malingering, especially in an attempt to obtain financial gain. Since the 1980s, more attention has been paid to the organic perspective due to improved neuroimaging techniques (Wrightson, 2000); however, some researchers still argue that any dysfunction in MHI, whether transient or permanent, is largely psychogenic (Alexander, 1995).

Psychological, contextual, and methodological factors affecting PCS

Females may be at increased risk for developing PCS even though men are more likely to sustain a head injury (Bazarian et al., 1999; Gasquoine, 1997; King, 1997; Rutherford et al., 1977; 1978; McCauley et al., 2001). A small but significant effect size was noted in a meta-analysis of eight studies on mild to severe head injuries, finding an overall outcome for women worse than for men (Farace & Alves, 2000).

One explanation for this might be related to differences in the mechanisms of injury. In particular, a greater percentage of females than males sustain head injuries in motor vehicle collisions (57% vs. 22%), whereas a greater percentage of males than females sustain head injuries while participating in sports (33% vs. 9%). Moreover, sports injuries exhibit less persistent sequelae than motor vehicle accidents (Bazarian et al., 1999; Bring et al., 1996). This difference might also be due to under-reporting of sports-related MHI because participants do not want to be removed from play (Carroll et al., 2004).

It seems reasonable to consider the elderly more susceptible to persistent sequelae, and this has been confirmed. In fact, the risk of persistent sequelae post-head injury is twice as high at age 40 as at age 30 (Fenton et al., 1993; Thornhill et al., 2000). There are, however, differences in injury types in youth and the elderly; younger adults are more likely to be injured in motor vehicle collisions, whereas older adults are more likely to be injured due to falls (Thurman et al., 1999). Pre-injury factors may also play a roll in any age-related differences because those injured in falls are more likely to have had prior stroke, cognitive impairment, and depression (WCB, 2003). Some other studies, however, failed to identify a significant relationship between age and outcome after head injuries (Alves et al., 1993; Breed et al., 2004). There are no clear explanations for the inconsistent relationship between age and PCS. Recently, some researchers have suggested that differences may be related to the level of injury severity; for example, seniors have longer PTA, a response that suggests a severe injury and a poorer ultimate outcome (WCB, 2003).

Another study examined contextual factors associated with PCS and found that individuals who had experienced significant life events (death, marriage, divorce, etc) in the year before injury more often developed PCS (Fenton et al., 1993). Such life events may hinder coping ability, possibly contributing to poorer recovery.
Some researchers have proposed that one's expectations of symptoms after a head injury causes recall bias—that is, because some individuals forget preinjury symptoms, they attribute all current symptoms to the trauma (Ferguson et al., 1999; Mickeviciene, 2004; Mittenberg et al., 2002; Suhr & Gunstad, 2002; 2005).

The relationship between pre-injury personality and MHI has been suggested as an explanation for persistent symptoms. Some researchers (Kraus, 1995; Parker, 1996) have suggested that personality change can be a consequence of MHI. In addition, individuals who sustain MHI may tend to take risks more than the general population (Cherpitel, 1999; Peterson et al., 1999; Szymanski & Linn, 1992).

Some researchers believe poor coping skills may explain prolonged PCS (Bohnen & Jolles, 1992; Karzmark et al., 1995; Ponsford et al., 2000; Ruff et al., 1996). However, a recent study by Rush *et al.*, (2004) investigating preinjury personality effects on outcome after MHI, involved a comparison of MHI and orthopaedic patients. Preinjury personality characteristics were not found to be different in the two groups.

The notable inconsistencies that exist in research on the etiology of PCS have recently been attributed, at least partly, to failure to divide MHI groups into those with and without PCS (Sterr et al., 2006). The study by Sterr et al. included 38 participants, who had sustained a MHI at least 12 months before there research project into those with PCS (29%) and those without PCS (71%). Matched controls were also included. The authors found that the subgroup with PCS exhibited greater disability on cognitive tasks than the subgroup without PCS. There was no significant difference between the control group and the subgroup without PCS; however, the sample size was relatively small. In addition, the authors did not address the fact that the subgroup with PCS was more likely to have received medical attention. This group was also likely to have had traffic incidents more than the subgroup without PCS whose injuries were more often caused by sports. As noted above, studies have shown that sport injuries are less likely to result in PCS than other forms of MHI (Bazarian et al., 1999; Bring et al., 1996). Despite this, the study offers an interesting perspective for further study.

Persistent symptoms after MHI can be associated with malingering, especially if litigation is involved (Binder & Rohling, 1996; Mickeviciene, 2002; Mittenberg, 2002; Reynolds et al., 2003; Paniak et al., 2002b). Binder and Rohling (1996) performed a meta-analysis to assess the relationship between potential financial gain and clinical outcomes after head injury. They found that financial incentives had a positive effect on the development of persistent PCS, especially in patients with MHI. Other important factors to consider include the following: response bias (Lees-Haley et al., 1997); alcohol abuse (Kraus et al., 1989); education level (Fraser et al., 1988; Kibby & Long, 1996); and psychiatric disorders, including panic disorder, obsessive-compulsive disorder (Evered et al., 2003; Fenton et al., 1993; Kraus, 1995; Rao & Lyketsos, 2002).

Organic explanations for PCS

Today, there is evidence that a MHI can result in brain damage and neuropathological lesions that are similar to those observed in other, more severe injuries, albeit to a different degree (McAllister & Arciniegas, 2002). A MHI can result in diffuse microscopic axonal injury caused by sudden acceleration/deceleration. Research on primates has demonstrated that acceleration without impact can cause brain damage (Gennarelli et al., 1982; Jane et al., 1985; Povlishock et al., 1983). Oppenheimer was the first investigator to identify similar findings in humans (1968). When he examined patients with MHI who had died from other causes, he found microscopic brain damage, micro-glial scars, and fiber degeneration.

Diffuse axonal damage is more common in the anterior region than in the posterior regions and in deeper structures than in more superficial structures. Microscopic stretching or shearing after a head injury tends to concentrate in the frontal (particular orbital) and temporal lobes and at the boundary between grey and white matter around the basal ganglia, periventricular zones, corpus callosum, and brainstem fiber tracts (Adams et al., 1989; Blumbergs et al., 1994; Graham et al., 2000; Polvishock et al., 1983).

Moreover, experimental MHI produces a neurochemical and neurometabolic cascades that disturb brain neurons (Giza & Hovda, 2001). The impact that causes a MHI triggers a cascade of events. Excitatory neurotransmitters, such as acetylcholine, glutamate, and aspartate, are released. These neurochemical changes usually take place within the first hours after the injury, but can be prolonged (Collins & Hawn, 2002; Dixon, 1993; Giza & Hovda, 2001). Research in animals has uncovered an association between the magnitude of acceleration-deceleration and the amount of diffuse axonal injury. Neuroimaging techniques, such as MRI, have demonstrated diffuse axonal injury, focal cortical lesions, and whole brain atrophy (Bigler, 2001; Blumbergs et al., 1994; WCB, 2004).

As mentioned previously, the prefrontal cortex, and especially the orbital frontal cortex, is particularly vulnerable to damage due to its close connection with the cribriform plate (a thin sheet of perforated bone located behind the nose area). Frontal lobe dysfunction can disrupt executive functions, sustained concentration and attention, organization, problem-solving, goal-oriented behavior, flexibility, and psychosocial behavior (for example, inappropriate behavior and aggression)

even in injuries that are classified as mild (Varney & Menefee, 1993). The temporal lobes (especially the anterior sections) are also commonly damaged during MHI. Because the temporal lobes play an important role in declarative memory, damage can result in difficulties related to the storage and retrieval of information (de Kruijk et al., 2001).

Apolipoprotein E

Apolipoprotein E (*APOE*) is a plasma protein mapped to the long arm of chromosome 19. With three primary alleles (ε2, ε3, and ε4), it acts as a key determinant in the transport of lipoproteins and cholesterol. *APOE* is primarily synthesized in the liver, but it is also found in abundance in the brain, where it is present in astrocytes and microglia, but not in neurons (Namba et al., 1991). *APOE* plays a major role in the redistribution of lipid and cholesterol transport during brain repair and synaptic plasticity (Mauch et al. 2001). We all inherit one allele from each parent, giving rise to six combinations of genotypes: ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4, and ε4/ε4. The frequencies of the different *APOE* alleles vary with populations, but the e3 allele is usually most dominant (Gerdes, 2003). In Sweden, the frequency of *APOE* ε3 is approximately 72%, *APOE* ε4 is 20%, and *APOE* is ε2 8% (Eggertsen et al., 1993).

The *APOE*, and specifically the ε4 allele, has emerged as a risk factor for adverse outcome after moderate and severe head injury (discussed more below). *APOE* ε4 is a well-known risk factor for Alzheimer's disease and other forms of dementia, including pugilistic dementia (punch-drunk syndrome) (Corder et al., 1995; Frisoni, 1994; Saunders et al., 1993). Furthermore, this increased risk of AD is related to the number of ε4 alleles: one ε4 allele increases the risk for AD about 2.5 times and two ε4 alleles increase the risk approximately eight times (Corder et al., 1995; Mausch et al., 2001). *APOE* ε4 has also been linked to vascular dementia in some (Frisoni et al., 1994; Kalman et al., 1998), but not all (Slooter et al., 1997) studies. In addition, some studies have demonstrated ε4 to be a risk factor for a number of other disorders, including multiple sclerosis (Oliveri et al., 1999) and coronary heart disease (Wilson et al., 1994). The influence of *APOE* on outcome after MHI is under intense investigation.

Dementia diseases

Dementia is a non-specific term that refers to several diseases characterized by progressive decline of cognitive abilities–including memory, thinking, learning capacity, language skill, perception, and judgment. Dementia may also cause pronounced behavioral and emotional disturbances, causing significant restrictions in daily life and progressively making independent living impossible. Dementia has been called a *late-life disease* since its prevalence increases with age and, for most causes of dementia, no cure exists. However, since treatment can slow progression of dementia, its early diagnosis is important (Dugué et al., 2003). The prevalence of dementia is very low before 65 years of age, affecting about 1%, but then increases steadily, to as high as 45% at age of 85 (Evans et al., 1992).There are many types of dementia; Alzheimer's disease (AD) is the most common form (55%) and vascular dementia (VaD) the second most common (about 20%). Although a detailed discussion of the pathophysiology of dementia disorders is outside the scope of this thesis, a brief summery of the major pathophysiological characteristics of the most common dementia disorder, AD, will be provided here (Dugué et al., 2003).

The two main principal histological findings of AD are amyloid plaques and neurofibrillary tangles. Amyloid plaques are clumps mainly composed of a protein peptide (or fragment) called beta-amyloid. They are found in the spaces between the brain's nerve cells. Beta-amyloid is cleaved from a larger protein, amyloid precursor protein (APP). In brains of patients with AD, the amount of beta-amyloid is much greater than normal, resulting in insoluble plaques (Simons et al., 2001). In AD, the degree of clinical severity reflects the amount of plaque formation. A normal brain has beta-amyloid, but in patients with AD (and in some other diseases, and, to some degree, even in normal aging) the amount of beta-amyloid in the brain is greatly increased. The reason for this increase remains unknown. The other principal feature, *neurofibrillary tangles,* are bundles of filaments found in neurons that are primarily composed of a protein called tau. In AD patients, the tau proteins, which normally stabilize microtubule tracks, change and microtubule structures collapse.

At the macroscopic level, brains of AD patients exhibit global atrophy–widening sulci, shrinking gyri, and enlarged ventricular spaces (Braak and Braak, 1994). The structures most affected in AD are the temporal lobes, particular the amygdala, the hippocampus, and the entorhinal cortex (Hyman et al., 1984). As the disease

progresses, pathology begins to develop in the parietal cortex and the frontal cortex (Braak and Braak, 1994).

The second most common dementia, VaD, often results from a series of blockages of small blood vessels that cause an interruption of blood flow, a condition that destroys enough brain tissue to decrease mental abilities. The size, location, and type of cerebral damage determine severity and type of clinical deficits. Recent research, however, has identified considerable overlap between these disorders. Clinically distinguishing between AD and VaD is difficult. Evidence suggests that these disorders fall within a spectrum between "pure" AD at one end and "pure" VaD at the other end (Kalaria, 2002). It is common to find cerebrovascular pathology in the pathogenesis of AD (Gorelick et al., 1996; Nolan et al., 1998; Pasquier et a., 1998; Skoog, 1998). Furthermore, as noted above *APOE* ε4 can be a risk factor for vascular diseases (Frisoni et al., 1994, 1995; Stengard et al, 1995; Treves et al., 1996).

Dementia and head injury

It has not been determined conclusively whether a history of head injury increases the risk for AD and other forms of dementia. Several studies have found that head injuries constitute a major risk factor for the development of AD and other forms of dementia (French et al., 1985; Guo et al., 2000; Graves et al., 1990; Mayeux et al 1995; Mortimer, et al., 1985; O′Meara et al., 1997; Rasmusson et al., 1995; Salib & Hillier, 1997; Schofield et al., 1997; the Canadian study of health and aging, 1994; van Duijn et al., 1992). However, some studies have not found this connection (Amaducci et al., 1986; Broe et al., 1990; Chandra et al., 1989; Ferini-Striambi et al., 1990; Fratiglinoni et al., 1993; Katzman et al., 1989; Launer et al., 1999; Mehta et al., 1999). A recent meta-analysis of 15 case-control studies found a significant association, with an increased odds ratio of 1.58 (95% CI: 1.21, 2.06) for men, but no increased risk for women (Fleminger et al., 2003).

Most of the literature focuses on moderate or severe injuries; however, only a few studies have included MHI in their sample. The MIRAGE case-control study (Guo et al*., 2000) investigated the risk of AD in head injury associated with loss of consciousness and without loss of consciousness. This study found that head injuries with loss of consciousness yield an odds ratio of 9.9 (95% CI: 6.5 to 15.1) for AD, and head injuries without loss of consciousness yield an odds ratio of 3.1 (95% CI: 2.3 to 4.0). Such case-control studies, however, have been criticized for

being vulnerable to recall bias. For example, an AD´s patient proxy may report a prior history of head injury more often than control subjects´ proxies (Chandra et al., 1989). Hence studies that rely on information collected before the onset of dementia would be preferred. Prospective studies minimize the risk of recall bias if trauma data are collected before the onset of dementia. In a study of a population-based historical cohort of 1776 US World War II veterans, Plassman et al. (2000) found an increased risk of AD and dementia following both moderate and severe head injury, but they did not find an increase risk following MHI. Another prospective study, however, found elevated risk of dementia following MHI although only for men (O'Meara et al., 1997).

Dementia, head injury, and Apolipoprotein E

Only a few studies have investigated the influence of *APOE* on dementia disorders following a head injury. In a study that examined whether AD was associated with head injury and the *APOE* ε4 allele, Mayeux et al. (1995) found a 10-fold increase with the combination of ε4 allele and prior head injury and only a 2-fold risk with ε4 alone. Results from the few studies that have been done since Mayeux et al.'s publication (1995) have been mixed. Some studies have found an increased risk (Koponen et al., 2004; Luukinen et al., 2005); other studies have found no increased risk at all (Mehta et al., 1999; Millar et al., 2003; Plassman et al., 2000); and one study revealed an increased risk for individuals *without* the ε4 allele (Guo et al., 2000). Luukinen et al. (2005) recently examined the risk of dementia after head injuries sustained as the result of secondary falls. For 9 years, this study prospectively followed 325 healthy seniors that were at least 70-year olds. After 9 years, 152 individuals were still part of the study. Eight of these individuals had sustained mild or moderate head injuries and 34 individuals had developed dementia. Among those eight individuals that sustained a head injury five developed dementia. In a subgroup including only individuals with 28 points or more in the baseline Mini-Mental State Examination test, ε4 was associated with a younger age of dementia detection. Luukinen et al. (2005) found the increased risk of dementia to be 7.68 (95% CI 2.33 to 25.3) among individuals with both the ε4 allele and a history of head injury. A major strength of this study was its population-based sample; however, the actual number of dementia cases was small.

Influence of Apolipoprotein E on head injury outcome

Growing evidence suggests that the *APOE* ε4 allele influences several outcomes following head injury, including longer period of unconsciousness following head injury (Friedman et al., 1999), cognitive decline in boxers and footballs player (Jordan et al., 1997), and decreased memory performance following head injury (Crawford et al., 2002). Animal studies have demonstrated that head injury in mice results in pronounced neuronal cell death in the hippocampus, accompanied by marked learning deficits and an outcome that is worse in transgenic mice with human *APOE* ε4 versus human ε3 or *APOE* knockout mice (Sabo et al., 2000).

Teasdale et al. (1997), using the Glasgow Outcome Scale (GOS) (Jennett & Bond, 1975), studied a group of patients who were admitted to a neurosurgery unit 6 months following mild to severe injury. Carriers of the ε4 allele had lower initial GCS scores than non-carriers (indicative of a poorer outcome), and controlling for this potential confounder increased the association further. Friedman et al. (1999) also reported a poorer initial outcome. Individuals with the ε4 allele were more likely to be unconscious for 7 days or longer than those without the ε4 allele. Furthermore, carriers of the ε4 allele were 14 times less likely to have a good outcome 6 to 8 months postinjury.

Lichtman et al. (2000) conducted a more objective measure of rehabilitation outcome, using the Functional Independence Measure (FIM) evaluation tool, in a study of 30 patients who had completed an acute inpatient neurorehabilitation program. They found ε4 to be associated with lower total and motor FIM scores, but they found no difference in cognition scores. FIM rates an individual's ability to perform daily life activities; however, it may be a too insensitive assessment tool to determine the influence of the ε4 allele, a possibility which was broached by the authors. Crawford et al. (2002) evaluated cognitive performance, especially memory variables, in a group of American military veterans 1 to 2 months after moderate to severe head injuries. The veterans with the ε4 allele exhibited significantly lower memory performance than the veterans without the ε4 allele.

Using GOS to measure outcome following predominantly moderate and severe injuries, more recent studies have found that ε4 was associated with an unfavorable outcome after 6 months (Chiang et al., 2003; Liaquat et al., 2002). However, some studies did not find the same results (Millar et al., 2003, Nathoo et al., 2003b). Nathoo et al. (2003b) evaluated a cohort of Zulus in South Africa with a particular

high frequency of the ε4 allele. Despite this, no differences were observed between carriers and non-carriers of the ε4 allele.

To my knowledge, there has been no prior study with a specific focus on outcome following MHI and its association with the *APOE* genotype. This is surprising because most injuries are mild and postconcussion symptoms do not seem to be associated with severity of injury. Most studies have focused on moderate or severe head injuries and have used relatively insensitive outcome measures, like the GCS, coma duration, FIM, or brief cognitive assessments (Chiang et al., 2003; Crawford et al., 2002; Friedman et al., 1999; Kerr et al., 1999; Lendon et al., 2003; Liaquat et al., 2002; Lichtman et al., 2000; Millar et al., 2003; Nathoo et al., 2003a; Teasdale et al., 1997).

The underlying mechanisms behind the association between *APOE* ε4 and poor outcome (post-head injury) are poorly understood; however, the ε4 allele has been associated with accelerated deposition of β-amyloid (Graham et al., 1995; Nicoll et al., 1995; Roberts et al., 1991; 1994) and has been conjectured to be involved in synapse plasticity after head injury (Chan et al., 1997; Sabo et al., 2000). A greater amount of β-amyloid has been found in carriers of *APOE* ε4 after head injuries (Graham et al., 1995; Nicoll et al., 1995; Roberts et al., 1991; Roberts et al., 1994). Animal models with experimentally-induced head injuries have exhibited excess accumulation of β-amyloid in axons that collapse within months to 1 year after injury (Iwata et al., 2002; Nakagawa et al., 1999; Pierce et al., 1998; Smith et al., 1997). Furthermore, carriers of the ε4 allele have been shown to have poorer coagulation and more intracranial hematomas (Liaguat et al., 2002). *APOE* ε4 is associated with poorer neuronal repair after trauma because cell cultures with the ε4 allele have exhibited a poorer outgrowth of neurons (Kutner et al., 2000). Alterations in neuronal cytoskeletons, increased oxygen susceptibility, and altered intra-cerebral cholesterol trafficking are other mechanisms that have been proposed (Kutner et al., 2000).

Taken together, some studies, but not all, support the hypothesis that the ε4 allele negatively affects outcomes following moderate to severe head injuries. Although there is no study that exclusively focused on MHI, some studies have included patients with either mild or moderate injuries where mild injuries predominated. In one study of 80 predominantly mild head injury patients, Liberman et al. (2002) found that those with the ε4 allele had poorer neuropsychological outcomes than those without. However, the difference between those with and without ε4

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decreased at the second assessment, making these results a bit difficult to interpret. Chamelian et al. (2004) extended these findings to six months following mild to moderate injuries, and used a more extensive neuropsychological test battery, but identify no relationship between outcome and the presence of the ε4 allele. It should be noted that both Chamelian et al. (2004) and Liberman et al. (2002) lacked control groups as well as preinjury data; hence it is unclear whether specific preinjury factors may have influenced findings.

AIMS

This thesis evaluates outcomes after MHI and the influence of the *APOE* genotype.

The specific aims are as follows:

1. To investigate neuropsychological performance before and after a MHI (Study I);

2. To estimate the self-reported fatigue before and after a MHI (Study II);

3. To evaluate whether MHI increase the risk for dementia after a MHI (Study III).

METHODS

All studies in this thesis are based on data from the ongoing Betula project, a prospective study on aging, memory, and health. For a detailed description of the Betula project and its design, sampling procedures, and battery of measures, see Nilsson et al. (1997; 2004). Briefly, the study consists of persons randomly selected from the population registry in Umeå, a city located in the northeast of Sweden, which had a population of about 100,000 inhabitants at the time of the first data collection. Participants were contacted by mail and participation was voluntary. Participants with severe visual or auditory handicaps, mental retardation, dementia, or whose first language was not Swedish were excluded from the sample.

The Betula project includes several independent samples, three of will be discuss here (S1, S2, and S3). Participants in S1 were part of the study at the beginning (1988-1990), and this sample also took part in all later data waves. S2 and S3 were included in the 1993-1995 wave; the older cohorts in S2 (i.e., age 75-85) and all cohorts in S3 were followed up at the third (1998-2000) and fourth data collection waves (2003-2005). S1, S2, and S3 consisted of ten age cohorts each (from 35-40 years to 80-85 years of age) with 100 participants in each cohort at the first assessment, except the oldest cohorts that did not fully reach 100 marks due to a problem finding participants that fulfilled the screening criteria. Table provides an overview of the design, a design that is inspired by Schaie (1965) and allows for the investigation of both longitudinal data and cross-sectional data.

Table 4

General overview of the Betula design

Test period	Sample	Age at test										
1988-90	*S1*		35	40	45	50	55	60	65	70	75	80
1993-95	*S1*		40	45	50	55	60	65	70	75	80	85
	S2	35	40	45	50	55	60	65	70	75	80	
	S3		40	45	50	55	60	65	70	75	80	85
1998-00	*S1*		45	50	55	60	65	70	75	80	85	90
	S2							70	75	80	85	
	S3		45	50	55	60	65	70	75	80	85	90
2003-05	*S1*		50	55	60	65	70	75	80	85	90	95
	S2							75	80	85	90	
	S3		50	55	60	65	70	75	80	85	90	95

The data in this thesis were derived from S1, S2, and S3 and included a total of 3,500 participants (see table 5).

Table 5
Characteristics of participants across studies

	Female/ Male, n	Age, y	MMSE, mean	Education, y	ε4 allele, %
Study I*					
MHI	17/17	56.6 (13.7)	27.9 (1.7)	9.7 (4.0)	32.4
Study II**					
MHI	11/17	55.7 (13.2)	28.1 (1.6)	10.2 (3.2)	39.3
Controls	22/34	55.7 (13.2)	27.8 (1.7)	10.2 (3.1)	39.3
Study III					
MHI	122/59	26.4 (2.4)	26.4 (2.4)	7.5 (2.9)	48
Controls	244/118	27.4 (1.7)	27.4 (1.7)	7.7 (2.9)	26.2

Note: SDs within parentheses.
* In Study I was non-injured age-, gender-, and education-matched *APOE* ε4 positive controls selected for each of the 11 persons in the *APOE* ε4 MHI group.
 ** Twenty-one participants in Study I also took part in Study II.

Assessments

At all test waves, the participants were examined at two test sessions, approximately one week apart. Each test session took between one-and-a-half to two hours for each participant. The first session consisted of a health examination and a few cognitive measures. A nurse conducted the health examination that included several health indicators: height, weight, vision, hearing, blood pressure, heart rate, and various blood sample testing (for example, *APOE* genotyping, blood glucose, cholesterol, and cortisol). The participants were also interviewed about general health, social, and economic issues, and critical life events. The cognitive examination concerned a broad variety of measures.

Among the subjective health variables, the following questions were asked:

Do you often feel fatigued?
Do you often feel depressed?
Do you often feel anxious?
Do you often have a sleeping problem?
Do you often feel lonely?

These questions could be answered by a "yes" or "no".

Years of education were collected at each data wave, but in this thesis only the baseline data were used as a measure of formal education. Age at baseline was also used.

Neuropsychological tests

Data from nine different neuropsychological tests were analyzed in Study I. These neuropsychological measurements were selected because they provide an overall reflection of cognitive functioning. In previous analyses, these tests have also shown to have moderate to high reliability and stability coefficients. Another criterion was that the chosen measures must have been part of at least two longitudinal test occasions to allow follow-up comparisons that make pre- and postinjury analyses possible.

Episodic memory measures:

* Free recall of actions and sentences: Participants were asked to memorize two lists of 16 sentences consisting of a verb and a noun (e.g., roll the pineapple, lift the book). The two lists differed in the mode of presentation. In one of the lists, the sentences were shown to the subjects and read one at a time by the tester. For the other list, the subjects were asked to perform the appropriate action with actual objects as the tester read the sentences. The nouns in the sentences were divided into four semantic categories. Directly after each presentation, the subjects were asked to try to orally recall the sentences in any order. The number of sentences recalled (correct verb and noun) from the two lists–with a maximum score of 16 for each condition (e.g., action vs. non-action condition) – was recorded.

* Recognition of actions and sentences: After a brief retention interval, the participants were presented with a list of 32 nouns–half were new and half were from the action/sentences studied earlier, with eight nouns from each condition (the other nouns were not studied and served as distracters). Number of hits minus false alarms from both conditions was entered in the analyses.

* Face recognition: Participants were shown 16 photographs (8 seconds per photograph) of children's faces. Below each photo, a fictional first and family name was typed. The participants were then asked to memorize the face and family name. After a delay of about 45 minutes, the participants were shown 24 photographs, 12 new ones and 12 old ones, randomly intermixed. They were asked to make an old/new judgment in response to each face. For each old target face they chose, they were asked to choose names from a list of four alternatives (first and family name). The number of hits, minus false alarms for faces, was recorded.

Working memory/Divided attention:

* Recall under conditions of Divided vs. Focused attention: Participants were presented with four word lists, each including 12 nouns, under different conditions (two s/item). They were instructed to remember the words and immediately after the presentation of each list recall as many words as possible. The different conditions were as follows: focused encoding/focused retrieval, focused encoding/divided retrieval, divided encoding/focused retrieval, and divided encoding/divided retrieval. Both condition and list order was counterbalanced. The distracter task consisted of sorting red and black playing cards into two piles according to their color. In this study, the measures used were focused encoding/focused retrieval and divided encoding/focused retrieval.

Semantic measures:

* Verbal fluency: Verbal fluency consisted of three tests in which participants were asked to generate as many words as possible in one minute. In the first test, the participants said aloud as many words as they could that begun with the letter "A". The second test was to generate five-letter words beginning with "M". The third test was to produce as many professions as possible beginning with the letter "B".

Visouspatial measures:

* *Block Design:* Subjects were asked to arrange red and white blocks in such a way that they formed the same pattern as a target pattern depicted on paper in front of them. This is a subtest of the Wechsler Adult Intelligence Scale-test battery (WAIS) to measure fluid intelligence and visuospatial ability (Wechsler, 1981). The measure used from this test was the raw score (with a maximum level of 51 points).

Mild head injury

Participants with MHI were retrospectively identified on the basis of a self-reported history of MHI. Specifically, identifying people who had suffered a MHI was done by screening their answers to a questionnaire that was part of the extensive health examination administered at all data waves. Repeated MHI has been found to have cumulative effects on neuropsychological functioning (Gronwall & Wrightson, 1974).

For inclusion in Studies I and II, the injury had to have occurred during the five years between the two test occasions so preinjury performance can be compared with postinjury performance. In Study III, the only restriction was that the injury did not occur five years before the diagnosis of dementia.

In Study I, local hospital medical records were found in 65% of all head injury individuals. In Study II, participants who did not have hospital medical records were telephoned and asked whether they had sustained a head injury. They were also asked how it had happened, in what year, and whether they had sustained more than one injury. If they had a history of more than one head injury, they were asked how many injuries they had sustained and when. They were asked whether they had sought help at a hospital or medical clinic. If they sought help at a hospital, they were asked how long they stayed. Finally, the participants were asked whether they had been unconscious and for how long.

Most injuries were accurately reported, and they were mostly mild. Study II included only those injuries that were considered mild according to the Mild Traumatic Brain Injury Committee of the American Congress of Rehabilitation (1993). For the participants who had no medical records associated with their head injuries, there was no independent data to confirm that they had suffered a MHI, leaving open the possibility that specific diagnostic criteria of MHI were not

fulfilled for some of these individuals. For this thesis, however, nothing indicated that these individuals had suffered a more severe injury. In such cases, records of hospitalization would likely exist. In the Betula study, the participants continued after sustaining their injury, an unexpected response for people who sustain severe head injuries.

Dementia diagnosis

Subjects were referred to a neuropsychological specialist if one or more of the following criteria were noted:

1. Signs of dementia observed by the nurse during the health examination;

2. A Mini-Mental State Examination (MMSE) score below 24 (Folstein, Folstein, & McHugh, 1975); and

3. A decline of three or more in MMSE score over a five-year period.

For those who underwent further examination, dementia was considered if they fulfilled the criteria according to the Diagnostic and Statistical Manual of Mental Disorders (4th ed., text rev.; American Psychiatric Association, 2000).

This study included 197 individuals diagnosed with dementia: 105 with AD; 65 with vascular dementia, 20 with unclassified dementia; 4 with Parkinson dementia; 2 with Lewybody dementia; and 1 with Frontotemporal dementia. To reduce the likelihood that these dementia diseases were present before sustaining a MHI, this study excluded those with dementia who had sustained a MHI within the five years before the reference year (n=16), reducing the final dementia group to 181 individuals.

APOE-genotyping

A polymerase chain reaction (PCR) was performed using 200 ng genomic DNA as a template in a 25 ml reaction mixture containing 20 pmol of PCR primers *APOE*-A (5′-TCC-AAG-GAG-CTG-CAG-GCG-GCG-CA-3′) and *APOE*-B (5′-ACA-GAA-TTC-GCC-CCG-GCC-TGG-TAC-ACT-GCC-A-3′) (Wenham et al.,

1991), 0.2 units (U) Taq DNA polymerase (Gibco BRL, Gaithersburg, USA), 1.0 mM MgC12, 75 mM TrisHCI ph9.0, 20 mM (NH4) 2SO4, and 10% DMSO. The PCR amplification consisted of 35 cycles of 30 seconds at 94°C, 30 seconds at 65°C, and 30 seceonds at 72°C. PCR products were digested using 5 units HhaI (Life Technologies) by incubating for three hours at 37°C. Bands were separated on a 5% agarose gel and visualized on a UV transilluminator after ethidium bromide staining. Alternatively, electrophoresis was performed using ExcellGel gels (Pharmacia) and the MultiphorII electrophoresis system (Pharmacia), and the bands were visualized by silver staining.

Statistical analysis

The statistical analyses were performed using standard statistical software, Statistical Package for the Social Sciences (SPSS). A P value of less than 0.05 was considered statistically significant.

* Study I: To determine the degree to which a longitudinal decline in cognitive performance might be specifically attributed to MHI, the following procedure was used. For each MHI subject, a score representing the change in performance over test occasion was calculated for each neuropsychological test. The non-injured subjects of each age cohort to whom a MHI subject belonged were used as controls after being matched for sex for each MHI subject. After converting all measures to standard (z) scores, the baseline/preinjury z-score for each MHI subject (zM=0) was compared to his/her postinjury z-score at retest relative to his/her own age and gender-matched control group (zM=0). For each MHI subject, this procedure controlled for age, sex, and practice effects and accounted for an above or below average preinjury level of neuropsychological functioning. Because a zero change between T1 and T2 for the non-injured control groups is normative (i.e., zM=0 for both test occasions), a z-score shift downward for a MHI subject indicates a worse than expected postinjury performance. Impairment was defined as a difference in z-score between pre- and postinjury test occasions of ≥1.0 SD. Differences in pre- and postinjury means among participants, divided in ε4 carriers and ε4 non-carriers, were assessed using a one-tailed paired sample t-test. The proportion of participants in the two allele groups that had a drop on two or more tests was evaluated by Fisher exact test.

* Study II: McNemar's test was used to examine differences in pre- and postinjury. The Fisher exact test was used to measure the difference between the MHI group and the control group.

* Study III: Matched Logistic Cox Regression Odds ratios were used to evaluate the risk for dementia. The subjects were divided into two subgroups, ε4 carriers and ε4 non-carriers. To assess the independent and combined odds ratios for dementia by MHI and *APOE* ε4 allele status, three dummy variables were constructed: subjects with the ε4 allele and no MHI; subjects without the ε4 allele and MHI; and subjects with both the ε4 allele and MHI. The subjects without the ε4 allele and no previous MHI were used as a reference group. Due to the small sample size in some clusters (e.g., ε4 carriers and MHI), analyses were done on the entire sample collapsed across dementia subgroups.

OVERVIEW OF STUDIES

Effects of APOE ε4 allele on neuropsychological functions after MHI (Study I)

As mentioned previously, the majority of people who suffer a MHI make a complete recovery without any residue of symptoms (Dikmen et al., 1987). However, a significant minority experience persistent symptoms. These persistent symptoms have been heavily debated and are described from an organic or psychological perspective, including emotional overlay or malingering (Alexander, 1995; King, 2003; Lishman, 1988). The *APOE* ε4 allele has been associated with a less favorable outcome following head injury. In Study I, we examine the relationship between neuropsychological outcome following mild head injury (MHI) and *APOE* genotype. Included in this study were 34 adults (17 men and 17 women, mean age of 57 at time baseline) and all had suffered a MHI in between the two test occasions (five years apart). Eleven of these were *APOE* ε4-carriers and 23 ε4 non-carriers. Their preinjury and postinjury performances on a battery of nine neuropsychological tests were compared with an age- and gender-matched control group.

The results showed no statistically significant differences in neuropsychological functioning between pre- and postinjury functioning, either for the MHI group or the control group. However, when the MHI group was classified by their genotype (e.g., into ε4 carriers and non-carriers), a significant difference was seen. It was found that ε4-carriers had significantly poorer postinjury performance than preinjury performance on two of the tests (Divided Attention, Face Recognition) and nearly significant decline (p<0.055) on one test (Free recall; Actions), whereas the pre-postinjury performance for *APOE* ε4 negative participants (n=23) was practically unchanged. There were no significant group differences in postinjury performance between participants with and without the ε4 allele, and neither group was impaired relative to controls. Thus these results show an unfavorable outcome for only ε4 carriers and only after conducting within-person analyses. The commonly used method of case-control group comparison may not have been sensitive enough to detect a subtle decline.

Fatigue before and after MHI: Pre-post injury comparison in relation to Apolipoprotein E (Study II)

Fatigue is a commonly reported sequela after a head injury and, as mentioned previously, often judged as one of the most troublesome sequelae because it significantly affects everyday life (LaChapelle & Finlayson, 1998). However, the prevalence of fatigue after mild head injuries is less studied and to our knowledge no study has investigated fatigue before after a MHI and in combination with the ε4 allele of the *APOE* gene. Since the within-person analysis from Study I showed that neuropsychological function was poorer for ε4 carriers than for non-carriers and controls, we predicted that the MHI group would report more symptoms of fatigue after rather than prior to MHI. We also predicted that this difference would be particularly salient in carriers of ε4 allele. To enable an association between MHI and *APOE* ε4, each participant who sustained a MHI within the five-year follow-up period was matched by age, gender, education, and genotype with two non-head injury controls. As in Study I, we used both a within-person and between-group design.

For the MHI group, symptoms of fatigue increased from 18% before injury to 46% after injury (p<0.03) (Table 3). No significant difference between the two measurement-points was observed for the controls: 27% reported fatigue at baseline and 21% at follow up. There was no difference at baseline/preinjury between the MHI and control group. At postinjury/follow up data point, the participants with MHI had higher fatigue than the non-injured controls (p<0.05).

In the subgroup with the ε4 allele and MHI (n=11), the percentage who reported fatigue increased from 9% to 55% (p=0.03). Pre- and postinjury analyses of non-carriers of the *APOE* ε4 allele (n=18) revealed no significant difference–22% vs. 39%. Differences between the two data points for controls, grouped by genotype, were not significantly changed; however, a between-group comparison between the MHI and the control group with ε4 allele showed a significant difference. The MHI group reported more often fatigue than the controls with ε4 allele (p=0.03).

As described previously, fatigue is often found to correspond with anxiety, sleeping difficulties, and depression (Katon & Walker, 1993; Fuhrer & Wessely, 1995; Walker et a., 1993). To account for these factors, we performed additional analyses. Anxiety, sleeping difficulties, depression, and loneliness were measured in the same ways as fatigue. The results showed no significant difference between

preinjury/baseline reports and postinjury/follow-up reports (see Table 6). Dividing groups according to *APOE* ε4 did not change the results.

Table 6
Reported frequencies (%) of symptom at baseline and at follow-up

Symptom Reported (%)	MHI group		Control group	
	Pre-injury	Post-injury	Baseline	Follow-up
Feel fatigue	17.8	46.4*	26.8	21.4
Feel anxiety	7.1	14.3	3.6	3.6
Sleeping difficulties	7.1	14.3	17.9	17.9
Feel depressed	3.6	7.1	5.4	5.4
Feel lonely	3.6	7.1	5.4	1.8

* $p < 0.05$

Increased risk of dementia following MHI for carriers, but not for non-carriers of the APOE ε4 allele. (Study III)

Although many studies have looked at the link between a prior history of head injury and the development of dementia diseases, the results are inconclusive. As was noted above, several studies have found head injury to constitute a major risk factor for the development of Alzheimer's disease (French et al., 1985; Graves et al., 1990), although other studies have found no greater risk than that expected by chance (Chandra et al., 1989; Fratiglinoni et al., 1993). Most studies examining the interaction of the ε4 allele and head injury in relation to the risk of dementia have had a retrospective design, based on the informant's recall of previous head injuries. Since such designs may suffer from errors in recall, studies that relay information collected before the onset of dementia are preferred (Rapoport & Feinstein, 2000). Study III investigated the joint effect the ε4 allele and previous MHI as risk factors for dementia diseases. On the basis of previous studies (Mayeux et al., 1995; Luukinen et al., 2005), we hypothesized that participants with the ε4 allele and prior MHI would have a higher risk of sustaining dementia diseases than controls without prior MHI. In addition, we predicted that MHI, in the absence of ε4 allele, would not lead to any increase in risk.

To examine the combined effects of head injury and genotype in the risk of dementia, dummy variables were constructed (head injury yes/no, ε4 allele yes/no). Subjects without both ε4 allele and head injury were used as references. Head injury that required medical attention was reported for 14% of the subjects in the dementia group and for 13% in the control group. Although head injury was reported more often among men than women, the difference was not significant. The odds ratios for those with both ε4 allele and past MHI (OR = 5.2, 95% CI 2.0 to 14.0) was greater than for those with ε4 but without MHI (OR = 3.0, 95% CI 1.9 to 4.7). MHI alone did not constitute any increased risk. An analysis restricted only to participants with a family history of dementia left the odds ratios unchanged (data not shown).

The present study suggests that MHI alone, in the absence of the ε4 allele, is not associated with increased risk for dementia diseases; however, the combination of MHI and the ε4 allele increases the risk for dementia five times in comparison with those lacking both factors. These results agree with other research (Luukinen et al., 2005; Mayeux et al., 1995) on more severe head injuries that suggest that MHI and the ε4 allele jointly increase the risk for dementia.

DISCUSSION

The general purpose of this thesis was to evaluate long-term outcomes after MHI, with special emphasis on neuropsychological functions (Study I), fatigue (Study II), and dementia diseases (Study III). A related objective was to examine the potential association between the *APOE* genotype and MHI outcome. The *APOE* ε4 allele has been associated with unfavorable outcomes after predominantly moderate or severe head injury, but little is known about its influence on MHI since few studies have addressed this issue. It was hypothesized that people with a history of MHI would have less favorable outcomes, and this could be true especially for carriers of the *APOE* ε4 allele.

The overall findings from the three studies presented in this thesis indicate positive outcomes for the majority of individuals suffering a MHI; however, when the MHI group was divided into subgroups based on the *APOE* genotype (i.e., people with or without the ε4 allele), it was found that the ε4 carriers were more likely to have unfavorable outcomes. In Study I, the findings indicated lowered neuropsychological performance after a MHI that occurred 1–5 years before testing for carriers of the ε4 allele, but not for non-carriers of the ε4 allele. Similarly, the results from Study II showed self-reported fatigue to be higher for individuals that had suffered a MHI compared to controls. In addition, for the MHI group there was a higher frequency of fatigue among ε4 carriers than non- ε4 carriers. Study III showed that ε4 carriers with a prior history of MHI had the highest risk of being diagnosed with dementia, but MHI did not increase the risk for dementia for non-carriers of the APOE ε4 allele. Collectively, these results show that *APOE* ε4 may influence self-reported function as well as objective measures of cognitive performance and dementia status after MHI.

To my knowledge, despite the fact that fatigue is a commonly reported symptom after head injury (Borgaro et al., 2005; Emanuelson et al., 2003; LaChapelle & Finlayson, 1998; Stulemeijer et al., 2006; Ziino & Ponsford, 2005; 2006), no prior study examines the relation between the ε4 allele and fatigue after MHI. Similarly, only a few prior studies investigated the influence of ε4 on neuropsychological outcome following MHI. One of these, Liberman et al. (2002), demonstrated a decline, although small, in neuropsychological performance for ε4 carriers 1 and 6 weeks post-injury. Chamelian et al. (2004) found no difference between carriers and non-carriers 6 months post-injury. Kutner et al. (2000) examined American

professional football players for *APOE* and cognitive performance, a study that found a subtle but significant post-injury decline in the same cognitive domains–attention and episodic memory–as our study. This pattern resembles findings reported in other head injury studies (Barth et al., 1983; Levin, 1990; Brown et al., 1994; Cicerone & Azulay, 2002; Stuss et al., 1989).

The post-injury increase in fatigue in Study II may be related to the reduction in divided-attention performance in Study I. This is because previous studies have shown that decreased ability to pay attention and concentrate can result in an intense feeling of fatigue (Azouvi et al., 2004; Belmont et al., 2006; Ziino & Ponsford, 2006). In Study II, we found that the increase in the level of fatigue was apparent after MHI even among participants without the ε4 allele, but still more pronounced for participants with the ε4 allele. This discrepancy between Study I and Study II might reflect that fatigue is a robust and general symptom after MHI and therefore increased both in ε4 carriers and non-carriers, while neuropsychological performance may be more subtle and only affected after MHI for carriers of the ε4 allele.

A couple of important differences between prior studies and studies I and II of this thesis should be highlighted. The most important one relates to the availability of preinjury data in our studies. When only a post-injury comparison was considered, we found no differences in Study 1. Rather, the observed differences in neuropsychological functioning were only visible in the within-person pre-post injury analysis. The importance of considering preinjury (baseline) data has recently been highlighted (Echemendia et al., 2001). Declines in neuropsychological performance associated with MHI are often subtle, and there is considerable individual variation in cognitive performance among healthy non-injured individuals, making interpretation of potential injury-related decreases in performance difficult (Barth et al., 2001). Several studies have begun to look at sport-related research to appreciate the influence of preinjury (preseason) functioning (for review see Iverson, 2005); however, the use of athletes is problematic because their high motivation to play even when injured may result in an underestimation of post-injury symptoms (Echemendia et al., 2001).

In contrast to most prior MHI studies, participants in this study were selected from a population-based, randomized sample. The vast majority of studies that investigate head injury outcomes have included patients from emergency departments or trauma centers, perhaps resulting in an overestimation of the

number of people at risk for a persistent poor outcome (McCullagh et al., 2003). Research on differences between those that are willing to participate in a study when asked and those who do not want to take part, indicate that people who are willing to participate have significantly more severe injuries with higher rates of using healthcare post-injury (McCullagh et al., 2003). There were no differences between preinjury demographic and health variables for those willing to participate and those unwilling. In addition, a preinjury matching of demographic and prior health variables did not predict outcome. The authors suggested that this indicates a striking recruitment bias in MHI research, which in turn would suggest that the commonly reported 10–20% of individuals with an unfavorable outcome is overstated. When people with no or few sequelae are unwilling to participate, a bias may result from the use of an in-patient population, a problem that has been highlighted by others as well (Gerberding et al., 2003). The pre- and post-injury design used in this thesis–where cases and controls were selected from the same population-based sample–has a low degree of this type of bias and should be particularly useful for studying the complex nature of MHI.

Head injury as a risk factor for dementia disorders is a controversial topic. The research is complicated by recall bias. Often, for example, a person other than the patient reports a prior head injury as a way to explain dementia; that is, informants for AD patients may more easily report a prior history of head injury than informants for control subjects (Chandra et al., 1989; Lye & Shores, 2000). Because the incidence of Alzheimer's disease and other forms of dementia exponentially increases in the elderly, finding age-matched non-demented healthy controls may be difficult (Graves et al., 1990). In this study, the very old healthy controls provided an opportunity for an unusually equitable comparison between dementia patients and controls. Furthermore, due to the prospective design of the study, information regarding prior head injury was collected before the onset of dementia, which reduced potential recall bias (Chandra et al., 1989).

The results from Study III showed a significantly increased risk of dementia diseases for individuals that had previously suffered a MHI *and* were carriers of the APOE ε4 allele. For the majority of MHI individuals (i.e., non- ε4 carriers), we found no evidence that head injury increased the risk for subsequent dementia. These findings are consistent with other research showing that prior head injury together with possession of the ε4 allele increased the risk more than each factor alone (Katzman et al., 1996; Mayeux et al., 1995). However, our findings question that MHI alone should be seen as a risk factor for subsequent dementia.

Unfortunately, the relative small number of individuals in Study III who were demented, had suffered a MHI, and were ε4-carriers made it impossible to distinguish among different dementia disorders. Further research is needed to differentiate within different subgroups of dementia (Bang et al., 2003). Nevertheless, several recent studies have reported links–at least partial ones– between the most common dementia disorders: Alzheimer's disease and vascular dementia. Risk factors for vascular diseases, such as high blood pressure, have been shown to be risk factors for Alzheimer's disease as well (de la Torre, 2000; Groves, et al., 2000; Laukka, et al., 2004). Autopsies of brains affected by Alzheimer's disease have revealed evidence of stroke or other cerebrovascular pathologic factors (Joachim, 1988; Kalaria & Ballard, 1999; Lim et al., 1999), and the frequency of the ε4 allele is overrepresented even for vascular dementia (Frisoni et al., 1994; Treves, et al., 1996). A recent study that compared the ε4 allele frequencies in Alzheimer's disease, vascular dementia, and controls revealed increased frequency of the ε4 allele in both dementia disorders, but no significant difference between the diseases was noted (Davidson et al., 2006). Two other studies have also reported an association between head injury and Alzheimer's disease as well as other dementia disorders (Salib & Hillier, 1997; Plassman et al., 2000). These studies indicate that the observed relationship between dementia, MHI, and ε4 may prove to be true even in a more detailed analysis considering dementia subtypes.

Taken together, the three studies in this thesis show that *APOE* ε4 status provides relevant information in analyses of outcomes after MHI with respect to neuropsychological functioning, fatigue, and risk for dementia. Although there is increasing evidence that ε4 plays an important role in neuronal remodeling, outgrowth, and protection (Blackman, 2005; Houlden & Greenwood, 2006), the mechanisms underlying this link between the *APOE* ε4 allele and a poor outcome after head injury is not entirely understood (Smith et al., 2006). It is suggested that ε4 increases neural susceptibility to handle neurotoxic agents, including amyloid beta peptides, age, head injury, oxidative stress, ischaemia, and inflammation (Lynch et al., 2003; Nathoo et al., 2003a). Others suggest that cerebrovascular or blood clotting are underling mechanisms that affect the brain's response to injury (Smith et al., 2006).

The studies in this thesis provided novel findings, but suffer from some limitations. First, although the data were obtained from a large-scale study, the groups were too small to analyze moderating influences of gender or age. Such factors may be important to consider. For example, a recent meta-analysis found head injury to be

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associated with Alzheimer's disease for males, but not for females (Fleminger et al., 2003). Elderly people and women are more often prone to injuries because of falls or other events that have lower velocities than velocities associated with motor vehicle accidents (Luukinen, 2005). This finding further underscores the potential relevance of considering gender and age in future studies.

The limited sample sizes in Study I and II should also be noted in relation to the reproducibility of findings. As pointed out by Collie et al. (2004), the effect in Study I was subtle, and a reduction of the number of measures analyzed would reduce the risk for statistical bias (Type 1 error). Therefore, a post-hoc analysis was performed with the four seemingly most sensitive tests. This analysis showed a post-injury decline by one SD on at least two of four measures in 4 out of 11 ε4 carriers (36%) and in 0 out of 23 non- ε4-carriers (Sundström & Nyberg, 2004). The post-hoc test revealed deficits in a third of the ε4 carriers, furthering strengthening the association. Nevertheless, the present notion of reductions in neuropsychological performance and increases in fatigue after MHI for ε4-carries should be replicated in larger samples.

Yet another limitation was the measure of fatigue, wherein the severity, intensity, impact on everyday activities, and dimensions of fatigue were not assessed. The same holds true for anxiety, sleeping difficulties, and gloominess. We did not evaluate the potential influence on quality of life after MHI for ε4 carriers, non-carriers, and controls. Other studies have found fewer reports of lower life quality after head injury (Emanuelson et al., 2003). Future research should explore the relationship among wellbeing, *APOE*, and outcome following MHI.

Because we did not analyze current medicine use, we can not rule out completely the influence of medicine on cognitive performance. We also lacked information on the *exact* duration between head injury and testing. Finally, we did not have access to medical records to confirm self-reports for all participants. With these limitations in mind, it is crucial to stress that the main finding of poor outcome after MHI for ε4 carriers agrees with the results of previous studies of outcome after more severe injuries (Kutner et al., 2000; Liberman et al., 2002).

Conclusions and further directions

The *APOE* ε4 allele is associated with increased fatigue, decline in neuropsychological performance, and elevated risk of developing dementia following MHI. Non-carriers of the ε4 allele with a history of MHI did not show any decline in neuropsychological performance or increased risk for dementia, but they did exhibit a higher frequency of fatigue postinjury than preinjury. Future research should continue to investigate the association among mild head injury, genetic factors, and various outcomes. Assessment of preinjury functioning appears critical for a full understanding of such associations.

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