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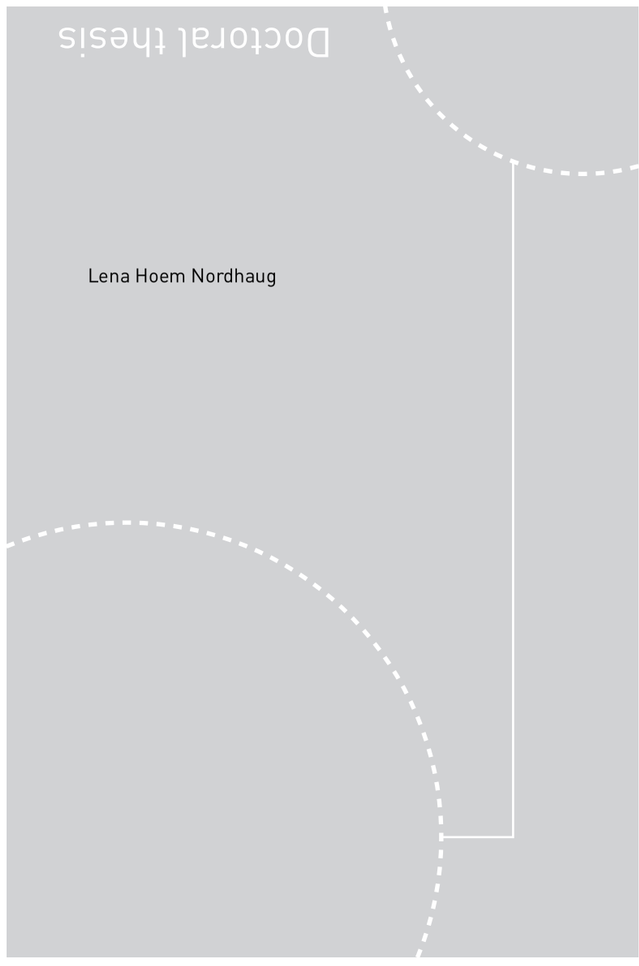
Lena Hoem Nordhaug

Headache Attributed to Traumatic Injury to the Head

Epidemiological Evidence and Natural Course

NTNU
Norwegian University of Science and Technology



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Thesis for the Degree of
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Trondheim, February 2019

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Hodepine tilskrevet hodeskade.

Over hele verden blir mer enn 50 millioner mennesker utsatt for hodeskader hvert år. Hodepine tilskrevet hodepine (HAIH) har blitt rapportert i flere studier som det vanligste symptomet etter hodeskader. Forekomsten av primær hodepine som f.eks. migrene og hodepine av spenningstype i befolkningen er imidlertid høy, og det er vanskelig å skille mellom HAIH og primær hodepine. Det er lite epidemiologisk bevis for at HAIH er en selvstendig hodepinediagnose til forskjell fra de primære hodepinene. Det overordnede målet med oppgaven var å undersøke om HAIH er en egen diagnose, ikke bare en primær hodepine som feiltolkes som HAIH.

I tre forskjellige studier undersøkte vi utbredelsen av hodepine hos personer som har vært utsatt for hodeskade og sammenlignet dem med personer uten hodeskade. I den første og tredje studien undersøkte vi i tillegg om ulike egenskaper ved personen eller selve hodeskaden kunne forutsi om noen hadde større sannsynlighet for å utvikle HAIH enn andre.

I den første studien sammenlignet vi svarene på hodepinespørsmål blant deltakere i den tredje Helseundersøkelsen i Nord-Trøndelag (HUNT3) som tidligere hadde vært innlagt på sykehus på grunn av en hodeskade, med resten deltakerne i studien, som ikke hadde vært innlagt på sykehus på grunn av hodeskade. Deltakerne med hodeskade hadde høyrere forekomst av hodepine, migrene, kronisk daglig hodepine og medikamentoverforbrukshodepine. Risikofaktorer for hodepine etter hodeskade var hodepine under sykehusoppholdet og kvalme eller svimmelhet i akuttmottaket.

I den andre studien brukte vi kohorten i den første studien som grunnlag, men vi inkluderte også hodepinedata fra HUNT2, forgjengeren til HUNT3. I denne studien inkluderte vi bare hodeskadedeltakere som hadde hatt hodeskaden sin mellom HUNT2 og HUNT3 og hadde svart på hodepinespørsmålene i begge studiene. Vi hadde dermed informasjon om hodepine før skaden og var i stand til å undersøke om deltakerne med hodeskade opplevde ny hodepine eller forverring av tidligere hodepine oftere enn kontrollgruppen. Deltakerne med hodeskade hadde høyere forekomst av ny hodepine og forverring av tidligere hodepine enn kontrollgruppen.

I den tredje studien rekrutterte vi personer utsatt for mild hodeskade (MTBI) fra akuttmottaket ved St. Olavs Hospital og Trondheim kommunale legevakt. Vi sammenlignet hodepineforekomst i MTBI-gruppen med en kontrollgruppe med lette ortopediske skader og en gruppe med friske kontroller. Alle deltakere svarte på et spørreskjema om hodepine det siste året, deretter etter 3 og 12 måneder. Økningen i odds for hodepine fra før skaden til de første 3 månedene etter skade var større for MTBI-gruppen enn for kontrollene, men endring i odds for hodepine fra før skaden til 3-12 måneder etter skaden, var ikke forskjellig mellom gruppene. Kvinner og pasienter med patologiske funn på CT eller MR hadde økt odds for å ha HAIH de første 3 månedene etter skaden. De som hadde opplevd flere hodeskader eller var under påvirkning av alkohol da de ble skadet hadde større odds for å ha HAIH 3-12 måneder etter skaden.

De to første studiene antyder at HAIH er vedvarende over flere år, mens den tredje studien bare finner bevis for akutt HAIH. Selv om vi ikke har en entydig konklusjon for vedvarende HAIH, er vårt svar på avhandlingens overordnede mål at hodepine etter hodeskade er en selvstendig diagnose.

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Finansieringskilde: NTNU

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Contents

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A warm thank you to **my parents** (that includes you, **Roy**) for always believing (at least pretending to believe) that I could do anything I set my mind to, and for teaching me that life is now, and that school and work is only one side to life.

Finally, special thanks to my husband and best friend **Axel Karl Gottfrid Nyman** for being an immense support and inspiration and for sharing my fascination for medicine and neurology, and to our beautiful son **Olav Gottfrid Nordhaug Nyman** for being an immense source of happiness and making me want to hurry home every afternoon.

List of Contributions

Paper I

Lena Hoem Nordhaug, Anne Vik, Knut Hagen, Lars Jacob Stovner, Torunn Pedersen, Gøril Bruvik Gravdahl, Mattias Linde. ***Headache related to previous head injuries: A population-based historical cohort study (HUNT).*** Cephalalgia. 2016 Oct;36(11):1009-1019.

Paper II

Lena Hoem Nordhaug, Knut Hagen, Anne Vik, Lars Jacob Stovner, Turid Follestad, Torunn Pedersen, Gøril Bruvik Gravdahl, Mattias Linde. ***Headache following head injury: a population-based longitudinal cohort study (HUNT)***. J Headache Pain. 2018 Jan 22;19(1):8.

Paper III

Lena H. Nordhaug, Mattias Linde, Turid Follestad, Øystein Njølstad Skandsen, Vera Vik Bjarkø, Toril Skandsen, Anne Vik. ***Change in headache suffering and predictors of headache following mild traumatic brain injury. A population based, controlled, longitudinal study with 12-month follow-up.*** (Manuscript)

Abbreviations and acronyms

AUDIT	Alcohol Use Disorders Identification Test
BMI	Body Mass Index
BFB	Biofeedback
CDH	Chronic Daily Headache
CGRP	Calcitonin Gene-Related Peptide
CI	Confidence Interval
CT	Computed Tomography
EGP	Erikson, Goldthorpe and Portocarero
GCS	Glasgow Coma Scale
HADS	Hospital Anxiety and Depression Scale
HAIH	Headache Attributed to traumatic Injury to the Head
HISS	Head Injury Severity Scale
HUNT	The Nord-Trøndelag Health Study
ICD	International Classification of Diseases
ICHD	International Classification of Headache Disorders
LOC	Loss Of Consciousness
MOH	Medication Overuse Headache
MRI	Magnetic Resonance Imaging
MTBI	Mild Traumatic Brain Injury
OR	Odds Ratio
OTC	Over-The-Counter
PCS	Post-Concussive Syndrome
PTA	Post-Traumatic Amnesia
PTSD	Post-Traumatic Stress Disorder
TAI	Traumatic Axonal Injury
TBI	Traumatic Brain Injury
TTH	Tension-Type Headache

Summary

Worldwide, more than 50 million people experience a head injury each year. Headache has been reported in several studies as the most common symptom following head injury, and headache attributed to head injury (HAIH) is claimed to be among the most common secondary headache disorders. However, the prevalence of primary headaches in the population is high and distinguishing HAIH from primary headaches is difficult. The available epidemiological evidence, confirming HAIH as a unique disease entity, is scarce. The overall aim of the thesis was to study whether headache after head injury is a unique disease entity separate from the most common headache disorders.

In three different studies, we investigated the prevalence of headache in individuals exposed to head injury and compared them with individuals without head injury.

In paper I, we evaluated the prevalence of headache among individuals previously exposed to head injury by comparing them to an uninjured control group in a population-based historical cohort study. We also studied predictors of headache in the head injury group. We included headache data from the third Nord-Trøndelag Health Study (HUNT3), a large population-based epidemiological study performed in Nord-Trøndelag in 2006-2008. This was linked with data from the participants' hospital records on exposure to head injury occurring between 1988 and participation in HUNT3. Participants in HUNT3 without head injury, according to hospital records, were used as controls. The head injuries were classified according to the Head Injury Severity Scale (HISS) and the International Classification of Headache Disorders (ICHD-3 beta). Binary logistic regression was performed to investigate the association between headache and head injury, controlling for potential confounders. The exposed group consisted of 940 individuals and the control group of 38,751 individuals. In the multivariate analyses, adjusting for age, sex, anxiety, depression and socioeconomic status, there were significant associations between mild head injury and any headache, migraine, chronic daily headache and medication overuse headache. Previous head injuries were significantly associated with headache suffering in HUNT3 only if they had been accompanied by headache during the hospital stay, nausea at admission or dizziness at admission. There was no significant association between headache suffering in HUNT3 and acute alteration in mental state at the scene or at admission, cranial fractures or traumatic intracranial pathology.

In Paper II, we used the cohort in Paper I as basis, but we also included headache data from HUNT2 which is a large population-based epidemiological study that preceded HUNT3, and was performed in 1995-1997. HUNT2 headache data was very similar to HUNT3 headache data. The study population in Paper II consisted of persons who had answered the headache questions in HUNT2 as well as HUNT3 and were hospitalized in the region due to a head injury occurring between HUNT2 and HUNT3. We thus had information about headache suffering before the injury and were able to investigate new headache suffering and exacerbation of previously reported headache. The exposed group consisted of 294 individuals and the control group of 25,662 individuals. In multivariate analyses, adjusting for age, sex, anxiety, depression, education level, smoking and alcohol use, mild head injury increased the risk of new onset headache suffering, stable headache suffering and exacerbation of previously reported headache.

Paper III describes a population-based, controlled, longitudinal study where we explored whether patients with mild traumatic brain injury (MTBI) had an increase in headache suffering after injury compared to controls. We also studied predictors of headache in the MTBI group. We recruited patients exposed to MTBI and controls with minor orthopaedic injuries from a trauma center and a municipal outpatient clinic, and community controls from the surrounding population. Information on headache was collected through questionnaires at baseline, 3, and 12 months post-injury. We used a generalized linear mixed model to investigate the development of headache over time in the three groups, and logistic regression to identify predictors of headache in the MTBI group. We included 378 patients exposed to MTBI, 82 trauma controls and 83 community controls. The increase in odds of headache from baseline to the first 3 months post-injury was larger for the MTBI group than for the controls. Odds ratios of change in headache from baseline to 3-12 months post-injury did not differ between the groups. Predictors for acute HAIH were female sex and pathological imaging findings on CT or MRI. Predictors for persistent HAIH were prior MTBI, being injured under the influence of alcohol, and acute HAIH.

The first two papers suggest that HAIH is persistent over several years, while Paper III only finds evidence for acute HAIH. Even though we don't have an unambiguous conclusion for persistent HAIH, our response to the thesis' overall aim is that headache after head injury is a unique disease entity.

1 Introduction

1.1 Headache

Headache is the most common neurological symptom in the population and constitutes a large social and economic burden for the global society as well as the individual.[64,104,122] Globally, it has been estimated that 47% of the adult population have an active headache disorder.[104] These disorders are shown to reduce quality of life,[47,89] reduce social functioning [16] and have a negative influence on family life.[47] They generate immense financial losses to society, both through direct costs such as medications, outpatient health care, hospitalization and investigations, but mainly through indirect costs such as work absenteeism and reduced productivity at work.[64] The latter is especially important for this group of disorders as they often affect subjects in their most productive years of life.[47] Taken together, this means that headache is among the most prevalent, burdensome and costly diseases of the world.

1.1.1 Primary and secondary headaches

Headaches can either be primary – the most common ones being migraine and tension-type headache (TTH) – or they can be secondary to another disorder, substance use or trauma. The Headache Classification Committee of the International Headache Society published a classification system for headache in 1988 (International Classification of Headache Disorders (1st edition), ICHD-1)[31]. This classification system was revised in 2004 (ICHD-2)[32], in 2013 (ICHD-3 beta)[33] and again in 2018 (ICHD-3)[34].

The ICHD-3 defines a secondary headache as a new headache that occurs for the first time in close temporal relation to another disorder that is known to cause headache, or

fulfils other criteria for causation by that disorder. This remains true even when the headache has the characteristics of a primary headache. The ICHD-3 also states that if a pre-existing primary headache becomes chronic, or is made significantly worse, in close temporal relation to such a causative disorder, both the primary and the secondary diagnoses should be given, provided that there is good evidence that the disorder can cause headache.

1.2 Traumatic brain injury

Traumatic brain injury (TBI) is a frequent and important global health issue with great socioeconomic consequences.[79] Worldwide, more than 50 million people experience a TBI each year, and it is estimated that about half the world's population will experience one or more TBIs over their lifetime.[80] The clinical manifestations of TBI vary widely and the variations are caused both by extent and mechanism of the damage. TBI is one of the leading causes of mortality in young adults and a major cause of death and disability across all ages in many countries.[79]

There is an increasing number of articles about veterans exposed to head injury during combat in war. However, the circumstances around the head injury, the injury mechanisms, and the comorbidity among those exposed to the head injury, are rather different from head injuries in the civilian population.[114,117] In military TBI the most common injury mechanism is blast injuries, something that is rarely seen in civilian populations outside war areas.[39] Furthermore, the prevalence of PTSD, depression and anxiety are higher in the veteran population than in the general population.[26,74] The papers presented in this thesis describe studies done on the civilian population. In the following, I am therefore going to focus on research done on the civilian population.

1.2.1 Pathophysiology and biomarkers in TBI

The pathophysiology of TBI is usually described according to moment of onset of the injury (primary or secondary injury) and the distribution of structural damage (focal or diffuse). The primary injury after TBI consists of damage resulting directly from the mechanical force affecting the cerebral tissues. The main primary injury types are haematomas, contusions and traumatic axonal injury (TAI). Secondary injury is initiated by the primary injury and consists of the cascade of cellular and molecular processes that cause further brain injury.[1] Secondary injury also refers to cerebral ischemia caused

by hypoglycaemia, hypotensive or hypoxic events, and raised intracranial pressure due to swelling or increasing haematomas.[1] Focal brain injury comprises subdural, epidural and intraparenchymal haematomas and contusions. Diffuse brain injury involves damage to axons, diffuse vascular injury, brain oedema and hypoxic-ischemic injury. After a head injury a patient can have both focal and diffuse brain injury. Axonal injury is considered to be the main injury type in mild TBI.[2]

After a TBI, uncontrolled release and leakage through damaged cell membranes of excitatory neurotransmitters, most notably glutamate, produces a cascade of cellular events including influx of calcium and sodium into neurons and glial cells, which has harmful effects (excitotoxicity). These damaging effects include failure of mitochondria and activation of enzymes that can lead to breakdown of the skeleton of the cells and irreversible axonal pathology. This can be followed by necrosis and in turn inflammation.[1] Some of the proteins involved in this processes can be used as biomarkers for neuroinflammation, injury to neurons or glial cells, damage to the blood-brain barrier or acute axonal injury.[57] These proteins can be measured either in cerebrospinal fluid or in blood. Two examples are S100-B and glial fibrillary acidic protein (GFAP), both peripheral blood markers for astroglial injury.[57,125]

1.2.2 Measurement of head injury severity

The literature is inconsistent as to the use of the two terms head injury and TBI. In 2010 The Demographics and Clinical Assessment Working Group of the International and Interagency Initiative toward Common Data Elements for Research on Traumatic Brain Injury and Psychological Health stated: "*TBI is defined as an alteration in brain function, or other evidence of brain pathology, caused by an external force*."[76] The term head injury, however, includes all traumas to the head. This means that the term head injury includes trauma where the brain may be unharmed, for example scalp lesions. It is, however, common to use severity-grading systems along with the term head injury, to give an indication of whether or not there has been an impact on the brain.

1.2.2.1 Glasgow Coma Scale (GCS)

The Glasgow Coma Scale (GCS) was developed in 1974 to assess depth of coma and impaired consciousness.[113] It is based on the observed response to stimuli regarding eye opening, verbal performance and motor responses. The scale ranges from a total score

of 3 to 15, where 3 is a patient with no responses to painful stimuli and 15 is a fully alert and oriented patient. Most head injury severity scales are based upon the GCS.

Table 1-1 The Glasgow Coma Scale

Eye opening 1-4	Verbal response 1-5	Motor Response 1-6
1 = None	1 = None	1 = None
2 = Opens to pain	2 = Incomprehensible sounds	2 = Extension to pain
3 = Opens to verbal command	3 = Words, incoherent	3 = Flexion to pain
4 = Opens spontaneously	4 = Confused	4 = Withdrawal from pain
	5 = Orientated	5 = Localizes pain
		6 = Obeys commands

1.2.2.2 Head Injury Severity Scale (HISS)

HISS classifies injury severity using the GCS score and presence or absence of amnesia, decreased alertness or memory in the medical history, focal neurological deficits and presence and duration of loss of consciousness (LOC). [102] HISS classifies head injuries into five severity levels: minimal, mild, moderate, severe and critical. In most cases, the categories severe and critical are combined and called severe. The presence or absence of complications appropriate for each severity interval is added as a second dimension to divide patients into groups with different risks, prognoses and treatment requirements. The classification system was used in the first Scandinavian guidelines for management of head injury from 2000, and is used in a modified form in the updated guidelines from 2013[43,116].

Table 1-2 Head Injury Severity Scale

Severity category	GCS interval	Complications
Minimal	15, no LOC or amnesia	Other indications for admission.
Mild	14 or 15 plus amnesia or LOC < 5 min or impaired alertness or memory.	Intracranial lesion on neuroimaging study
Moderate	9 – 13 or LOC ≥ 5 min. or focal neurological deficit	Intracranial lesion on neuroimaging study
Severe	5 – 8	Brainstem haemorrhage or effacement of brainstem cisterns or age ≥ 70 years
Critical	3 – 4	Loss of pupillary reflexes or severe non-neurological injuries or age ≥ 70 years

LOC: Loss of consciousness

1.2.2.3 WHO criteria for Mild Traumatic Brain Injury (MTBI)

The WHO's task force on mild TBI (MTBI) (2004) stated that MTBI is an acute brain injury resulting from mechanical energy to the head from external physical forces and recommended the following operational criteria for clinical identification of MTBI:

> 1) One or more of the following: confusion or disorientation, loss of consciousness for 30 minutes or less, post-traumatic amnesia for less than 24 hours, and/or other transient neurological abnormalities such as focal signs, seizure, and intracranial lesion not requiring surgery;
>
> 2) Glasgow Coma Scale score of 13–15 after 30 minutes post-injury or later upon presentation for healthcare.

These manifestations of MTBI must not be due to drugs, alcohol, medications, and they must not be caused by other injuries or treatment for other injuries or by penetrating craniocerebral injury.[10]

1.2.2.4 Head injury severity levels in the International Classification of Headache Disorders, 3rd edition (ICHD-3)

ICHD-3 has specific criteria for the diagnosis of headache attributed to traumatic injury to the head.[34] It classifies injury severity based upon GCS score, LOC, amnesia, alteration in level of awareness, the presence of imaging evidence of traumatic brain injury and symptoms and signs of concussion. The classification distinguishes between headache attributed to mild traumatic injury to the head and headache attributed to moderate or severe traumatic injury to the head.

Table 1-3 Head injury severity levels in ICHD-3

Severity category	
Mild	**Head injury fulfilling both of the following:** *1. Associated with <u>none</u> of the following:* a) LOC >30 minutes b) GCS score <13 c) PTA lasting >24 hours d) Altered level of awareness for >24 hours e) Imaging evidence of a traumatic head injury such as skull fracture, intracranial haemorrhage and/or brain contusion. *2. Associated, immediately following the head injury, with one or more of the following symptoms and/or signs:* a) Transient confusion, disorientation or impaired consciousness b) Loss of memory for events immediately before or after the head injury c) Two or more other symptoms suggestive of mild traumatic brain injury: nausea, vomiting, visual disturbances, dizziness and/or vertigo, gait and/or postural imbalance, impaired memory and/or concentration.
Moderate or Severe	**Injury to the head associated with <u>at least one</u> of the following:** a) LOC >30 minutes b) GCS score <13 c) PTA lasting >24 hours d) Alteration in level of awareness for >24 hours e) Imaging evidence of a traumatic head injury such as skull fracture, intracranial haemorrhage and/or brain contusion.

LOC: Loss of consciousness, GCS: Glasgow Coma Scale, PTA: Post-traumatic amnesia

1.2.3 Mild traumatic brain injury and Post-concussive syndrome

Mild traumatic brain injury (MTBI) represents 80%-90% of all TBI and has been estimated to affect more than 600 adults per 100,000 each year.[11] The patients may develop relevant post-concussion symptoms including, but not confined to, headache, dizziness or vertigo, fatigue, irritability, disordered sleep, and memory and concentration problems.[80] This cluster of symptoms is referred to as post-concussive syndrome (PCS) and is most commonly associated with MTBI, but it may also occur after moderate and severe TBI.[80] Patients with MTBI may also have anxiety, depression and post-traumatic stress disorder.[80] Post-concussion symptoms pose particular challenges for outcome assessment because their occurrence depends on complex interactions between physiological, psychological, and social factors. Furthermore, they are not entirely specific to TBI as they can occur in patients with a range of different disorders or in healthy individuals.[12,80] Because these symptoms are not specific to patients

exposed to TBI and because higher rates of symptom have been reported in cases with potential for secondary gain, there is some controversy connected to the syndrome, especially in its protracted form.[18,22]

1.3 Headache Attributed to traumatic Injury to the Head (HAIH)

Headache attributed to traumatic injury to the head is, according to ICHD-3, one of the most common secondary headache disorders.[34] HAIH is defined in ICHD-3 as a headache disorder with no defining clinical characteristics that starts within seven days of trauma or injury, or within seven days after regaining consciousness, if the head trauma or injury resulted in loss of consciousness. HAIH is defined as persistent if it continues beyond three months (Figure 1.1).

Acute headache attributed to traumatic injury to the head

Headache of less than three months' duration caused by traumatic injury to the head.

A. Any headache fulfilling criteria C and D
B. Traumatic injury to the head has occurred
C. Headache is reported to have developed within seven days after one of the following:
   a. the injury to the head
   b. regaining of consciousness following the injury to the head
   c. discontinuation of medication(s) impairing ability to sense or report headache following the injury to the head
D. Either of the following:
   a. headache has resolved within three months after its onset
   b. headache has not yet resolved but three months have not yet passed since its onset
E. Not better accounted for by another ICHD-3 diagnosis.

Persistent headache attributed to traumatic injury to the head

Headache of more than three months' duration caused by traumatic injury to the head.

A. Any headache fulfilling criteria C and D
B. Traumatic injury to the head has occurred
C. Headache is reported to have developed within seven days after one of the following:
   a. the injury to the head
   b. regaining of consciousness following the injury to the head
   c. discontinuation of medication(s) impairing ability to sense or report headache following the injury to the head
D. Headache persist for > 3 months after its onset.
E. Not better accounted for by another ICHD-3 diagnosis.

Figure 1.1 Diagnostic criteria for acute and persistent HAIH in the ICHD-3

1.3.1 Epidemiology of HAIH

Headache has been reported in several studies as the most common symptom following traumatic brain injury[17,18,60,61,67] and is reported to occur in 25-78% of persons with recent mild TBI.[9,38,88] A multicentre, clinic-based study from the USA investigated new or worse headaches compared to pre-injury in persons with MTBI and found that the

proportion of participants who experienced headache sometime during the follow-up period (cumulative incidence) was 91% over one year.[67] Persistent HAIH is reported in several studies,[18,38,67] and is claimed to last more than one year in one out of five cases.[21,65,114] However, this epidemiological data on HAIH is from uncontrolled studies or literature reviews. These studies can be valuable contributions to the description of the HAIH population, but as they have no control group these studies are very vulnerable to bias and are thus not useful in the evaluation of a possible association between head injury and headache and must therefore be read with caution. Furthermore, the incidence and prevalence of HAIH is difficult to determine accurately because not all persons seek medical assistance after their head injury.[73,98]

1.3.2 HAIH phenotypes

Although HAIH is defined as a secondary headache with no defining clinical characteristics, it often presents clinical features similar to the most common types of primary headache.[60] More specifically, it has been shown that, based on clinical characteristics, HAIH usually does not differ from migraine or TTH.[42,60,114] A number of studies have reported TTH as the most common phenotype,[3,42,60] while several studies published in recent years report migraine as the most common headache phenotype after head injury.[38,62,66,67,118] Many patients have more than one headache phenotype after head injury.[9,14] Also other much less common phenotypes, including cluster headache, hemicranias, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), nummular headache and primary stabbing headache have been reported following injury to the head.[78]

1.3.3 Pathogenesis of HAIH

Acute headache after head injury might arise from soft tissue damage or damage to bone or blood vessels, including intracranial bleeding causing increased intracranial pressure and irritation of the meninges, referred pain from the neck, or release of pain fibre neuropeptide activating substances.[86] Persistent headache after head injury, however, has no known pathogenesis, but there are some hypotheses, which are presented below.[86]

In previous studies it has been suggested that head injury can cause a cascade of biochemical changes that are similar to the biochemical conditions in migraine and that

this may explain the occurrence of headache following a head injury.[27,42,86] Some allege that because HAIH can share clinical characteristics with migraine and TTH, HAIH is likely generated by the same processes that cause primary headaches. This concept is further supported by the reported effectiveness of triptans, a group of medications commonly used as abortive treatment against migraine, for relieving HAIH in patients with migraine-like phenotype.[19] However, in a study from 2017, the authors compared 28 individuals with persistent HAIH following MTBI with 28 individuals suffering from migraine with regard to cortical thickness, surface area and curvature measurements calculated from MRI T1-weighted sequences.[96] The authors found differences in structure within several brain regions which all have been previously demonstrated to participate in pain processing.[96] According to the authors, their study suggests that the pathophysiology of persistent HAIH might be different than that of migraine.[96] The authors of a prospective, repeated measures study investigated neurophysiological alterations following concussion using brain network activation analysis of brain activity. They found that patients with migraine-like HAIH showed decreased brain network activation and deviation from usual brain network activity compared to patients exposed to concussion, but without HAIH, and controls without concussion.[51]

Following TBI, inflammation is rapidly induced as a response to the primary injury to brain tissues.[126] Inflammatory activity that involves persistently activated glial cells, presents a plausible common link between the pathophysiology of TBI and the development of HAIH. A recently published study of rats with induced concussion demonstrated that pain and headache related behaviours can be alleviated by chronic treatment with an anti-CGRP (calcitonin gene-related peptide) monoclonal antibody, suggesting a peripheral process linked to the sensory neuropeptide CGRP as an underlying mechanism.[8] However, the degree to which inflammation plays a role in the development of persistent HAIH cannot be evaluated in isolation from all the other changes that occur in the brain following TBI.[72]

Sleep disturbances, mood disturbances and psychosocial stressors following head injury can plausibly influence the development and persistence of headache.[5,95,112]

Overuse of headache medications may contribute to the persistence of headache after head injury through the development of medication-overuse headache (MOH).[37,60] MOH is defined in ICHD-3 as a headache occurring on 15 or more days per month developing as a consequence of regular overuse of acute or symptomatic headache medication (on

10 days or more, or on 15 days or more per month, depending on the medication) for more than 3 months.[34]. MOH can occur with both over-the-counter and prescription pain-relief medications as well as overuse of the so-called triptans (selective 5-$HT_{1B/1D}$ agonists). In a Norwegian study, investigating the prevalence of secondary chronic headache, about half of the individuals with CDH caused by HAIH had a co-occurrence of MOH.[127] In a retrospective study from the USA, the authors found that the majority (70%) of the participants, recruited among adolescent patients referred to a headache clinic with HAIH following concussion, also had MOH.[37]

1.3.4 Predictors for persistent HAIH

1.3.4.1 Preinjury - and demographic factors

The prevalence of primary headache, mainly migraine, is known to be higher among women than men.[47]

This difference between men and women has also been studied for HAIH. Most studies have found female sex to be a risk factor for developing HAIH,[18,38,46,81] while others have found no differences between the sexes.[67]

Age also has an impact on the prevalence of primary headache in the general population. For both sexes the prevalence of headache increases with age until a peak is reached between 30-50 years, before it again decreases with age.[47] Few studies have examined this in HAIH, but a study from USA in 2014 showed that individuals over age 60 were less likely to report headache after head trauma.[67] Others have found no difference in risk with age.[38,81,105]

Several studies have reported that previous history of headache is a risk factor for persistent HAIH,[38,78,105,119] but a prospective study from Denmark was not able to verify this.[46] The authors from the Danish study found that patients suffering from headache before the trauma were no more at risk of having post-traumatic headache than patients who did not suffer from headache before the trauma.[46] They did, however, find that patients who experienced an increase of already existing pre-traumatic headache used more analgesics than patients first suffering from headache after the head injury.[46] Their findings could be in support of the hypothesis of MOH as one of the mechanisms of HAIH.

Insomnia and other sleep disturbances are often seen as comorbidities to headache.[91] It is not known whether headache is the cause of, or the result of, disturbed sleep. Studies suggest that these disorders might not only be a risk factor for each other, but that they also reciprocally influence and exacerbate the severity of each other.[100] Also in HAIH research, a relationship has been shown between sleep and HAIH, and insomnia and other sleep disturbances are suggested as predictors of prolonged HAIH recovery.[41]

History of depression, history of anxiety and PTSD have been shown to be predictors for development of post-concussion symptoms and HAIH, but are best described among soldiers injured during combat in war.[90,114,115,117,121]

1.3.4.2 Acute symptoms

A prospective study from the Netherlands indicated that the presence of nausea in the emergency room after mild TBI was strongly associated with the severity of most post-traumatic complaints, including headache, after six months; however, headache and dizziness in the emergency room were not significantly associated with persistent headache.[17] In a population based study from Norway, the authors found no association between having had headache the day after head injury and chronic headache last year 22 years later.[81] Headache in the emergency room has, however, been shown to be a positive predictor for development of PCS at 3 and 6 months post-injury.[13,24]

1.3.4.3 Head injury severity and intracranial pathology

It has not been possible to establish evidence of a direct dose-response relationship regarding head injury severity and the development of HAIH.[15,81,92] There are, however, several reports of an inverse dose-response relationship, i.e. mild head injury seems to cause persistent HAIH more frequently than moderate or severe head injuries.[14,97,114,118,123].Nevertheless, it is recognized that traditional head injury severity classifications have limited power in predicting long term functioning.[110]

It is debated whether intracranial pathology in MTBI gives more symptom reporting than MTBI without intracranial pathology. A prospective study from Finland compared symptom reporting, including headache, at 3-4 weeks after complicated (trauma-related intracranial abnormality) and uncomplicated (no findings on CT or MRI) mild TBI. The study, using the Rivermead Post-Concussion Questionnaire, showed no significant difference in symptom reporting between the groups with complicated and uncomplicated mild TBI.[45] However, in a recent study from Korea, the authors found

that HAIH occurred more frequently in patients with minimal traumatic intracranial haemorrhage after a head injury than in those without.[40]

1.3.4.4 Multiple head injuries

The authors of a recent review on factors associated with sports-related HAIH states that those with multiple concussions experienced HAIH more frequently than those with single concussions.[94] They also reported headache of greater severity. A study that examined the risk of chronic daily headache (CDH) following head or neck injury found that the odds of CDH increased with the number of lifetime head or neck injuries.[15] In a study aiming to predict which head injury patients were at risk for developing persistent post-concussion symptoms, multiple head injuries was one of the positive predictors.[121]

1.3.4.5 Litigation

It is widely debated whether a patient's expectation of headache following head injury or litigation promotes its development and persistence.[27] A study done in Lithuania, where there was both a lack of insurance against personal injury and little expectation of developing headache after head injury, could not corroborate the existence of persistent HAIH.[105] In a sample of 86 patients with MTBI referred to a hospital-based concussion clinic in Canada, the authors found that patients who were involved in litigation reported more post-injury symptoms than patients in the MTBI group who were not involved in litigation.[58] The level of post-injury symptoms was measured as total score on the British Columbia Post-Concussion Symptom Inventory (BC-PSI) and headache was not considered as an isolated outcome.[58] However, symptom resolution does not typically occur following legal settlements.[21,85] More knowledge is needed before one can conclude whether litigation is a true predictor of HAIH.[27]

1.3.5 Timing of HAIH onset

One criterion in ICHD-3 for classifying a headache as attributed to traumatic injury to the head, is the onset of headache within seven days of the injury or within seven days after regaining consciousness.[34] However, the authors of several studies have argued that this criterion may be too strict.[38,68,70] In a prospective study from the USA, the authors state that this criterion leads to an underestimation of the rate of post-traumatic headache.[38] They found that 28% of new headaches were reported *after* the initial evaluation that was performed prior to or within 1 week after discharge from inpatient

rehabilitation.[38] The authors of ICHD-3 state that even though this seven-day interval is somewhat arbitrary, and some experts argue that headache may develop after a longer interval, there is not enough evidence to change this criterion.[34] They encourage research on an alternative set of diagnostic criteria called "*Delayed-onset persistent headache attributed to mild/ moderate or severe traumatic injury to the head*" that allow for headache to begin beyond seven days and up to three months after the injury.[34]

1.3.6 Epidemiological challenges in HAIH

Headache is a very common disorder, and many of the persons who experience an MTBI will therefore be headache sufferers even before being exposed to an MTBI. This makes research on HAIH challenging and there are several types of bias one should be aware of. In a prospective study where the first meeting with the participant is after exposure to the head injury, recall bias can be a problem.[44] Participants might tend to under-report headache before their head injury because they regard their headache as a consequence of their head injury. In studies with lack of controls, it is difficult to distinguish a pre-existing headache from HAIH.[18,84] If the study group reports pre-injury headache prevalence below the headache prevalence in the general population, there is reason to suspect such bias. To handle the issue with bias it is necessary to include a control group so that the change in headache can be compared to a group without exposure to head injury.[58] Whether this control group should be community controls or have injuries other than to the head, depends on the intention of the study. If the intention is to investigate whether MTBI is a risk factor for development of headache regardless of underlying mechanisms, a community control group is more appropriate [71]. However, a control group with injuries other than TBI could be the preference, if the intention is to investigate whether head injury could trigger headache through mechanisms the participants will experience regardless of which part of the body is injured.[71]

The majority of studies published on HAIH are based on data from hospitals or cases referred to specialist clinics due to post-injury symptoms.[84] Hospitalization of patients with MTBI is becoming less common and a population-based design including both non-hospitalized and hospitalized patients is therefore important in order to avoid selection-bias.[35] When evaluating headache following head injuries in specific groups – such as veterans or patients at a rehabilitation clinic – it is important to put the subjects' headache status in context of the typical headache status in that specific group. Generalization of the results to the general population, on the other hand, may not be

advisable. If the intention of the study is to investigate whether or not HAIH is a true secondary headache entity and not a primary headache misattributed to head injury, it is essential to choose a population-based design.

In 2014, the International Collaboration on Mild traumatic brain injury Prognosis (ICoMP) performed a systematic review of studies on self-reported prognosis in adults after MTBI.[12] Only 29% of the 173 eligible articles on MTBI prognosis in adults were evaluated as having a low risk of bias.[12] This systematic review demonstrated that more studies of high quality are needed in this field to ensure the best possible care for patients experiencing a head injury.

1.3.7 Treatment of persistent HAIH

Management of HAIH is difficult and complex because of the many potential underlying factors and multiple comorbid conditions. There are few good studies on the treatment of HAIH. Only very few of the studies are randomized controlled trials, most studies are observational.[27] While we await better knowledge of how to best treat HAIH, experts suggest using treatment strategies with proven efficacy against the primary headache that it most resembles.[27,60,120]

As mentioned previously, medication overuse may be a factor in the development and prolongation of HAIH.[37,60] It is therefore crucial that the patients not only receive acute (abortive) treatment for their headache, but also information to enable themselves to avoid the development of MOH and, when needed, prophylactic treatments.

1.3.7.1 Abortive treatment

Although it is common to recommend treating HAIH as the primary headache it most resembles, documentation of the effect of triptans, a well-documented abortive treatment against migraine, is limited.[78] In a retrospective observational study of US soldiers from 2011, 70% of HAIH subjects who used a triptan experienced reliable headache relief within 2 hours, while 42% of subjects using other headache abortive medications (i.e. analgesics) experienced relief.[19] 95% of the participants reported having migraine type headache.[19]

1.3.7.2 Preventive treatment

When preventive treatment is used against migraine, it is recommended that the patients keep a headache diary for documentation of effect. The medication should be

tried in adequate dosage for 3 months before evaluating the effect.[23] If the treatment is effective, one may nonetheless try to discontinue the medication after 6 months for evaluation of its necessity.[23] The same procedure is probably useful also in the management of HAIH.

Non-pharmacological treatment

Because of the complex nature of HAIH, where several psychological, cognitive and physiological symptoms may contribute to the headache, it is considered useful to apply a multifactorial approach to its treatment. In situations where the patient is suffering from depression or anxiety, including psychoeducation about the role of emotional factors on pain responses could be important for improvement.[25] However, in a randomized controlled trial from 2014, ninety patients with HAIH according to ICHD-2 criteria were enrolled from the Danish Headache Center.[50] The patients were randomized to either a waiting list group or to cognitive behavioural therapy (CBT). The latter had no significant effect on headache, but a minor significant effect on psychological distress according to The Symptom Checklist (SCL-90-R).[50]

Biofeedback (BFB) is a self-regulation technique where the users are attached to specific devices and receive feedback on selected physiological parameters such as fingertip temperature or muscle tension to better control their autonomic responses.[109] Although several studies have shown that BFB and relaxation therapy have preventive effects on both migraine and TTH,[56,109] there are no randomized controlled trials of BFB as treatment of HAIH. The few studies available demonstrate varying effectiveness. Some of them have shown positive results, but suffer from low statistical power.[111] Some of the trials combined the use of BFB and other treatment modalities, such as medication and educational sessions, which makes the interpretation of the isolated effect from BFB difficult to interpret. [30,75,111].

Because of the high prevalence of comorbid conditions, management of HAIH should include an evaluation of the patients' sleep patterns and psychologic status.[60]

Pharmacological treatment

Amitriptyline is one of the more commonly studied medications against HAIH.[78] A retrospective observational study of adolescents with mostly sport-related concussions reported that 82% of those who took amitriptyline experienced improvement of their headache symptoms. Twenty-three percent reported side effects and the most commonly reported side effect was sedation.[7] However, in a retrospective observational

study from 2011 of 100 US soldiers with MTBI, only topiramate gave a significantly lower headache frequency after 3 months (48% of subjects achieved a 50% or greater reduction in headache frequency). Amitriptyline, valproate or propranolol did not give significantly lower headache frequencies. However, the statistical power in this study was low because of small sample sizes in all groups.[19] Valproate, a medication used in preventive treatment of migraine, was also studied in a retrospective study of patients with chronic daily headache (CDH) after MTBI[87]. The authors studied headache frequency and intensity after at least 30 days of treatment with valproate. Other treatments with analgesics, NSAIDs, chiropractic, or physical therapy were allowed during this time. 44% of the subjects had a 24-50% improvement, and an additional 16% had greater than 50% improvement with these interventions.[87]

Onabotulinum toxin A (Botox®) injections were evaluated in treatment of HAIH among American soldiers with MTBI in a retrospective case series of 64 subjects.[124] The most common headache type among the participants was CDH with combined migraine and TTH phenotype. 63% of study patients received Onabotulinum toxin A injections and 64% reported their headaches as "better" and 28% reported that headaches were unchanged, with 8% as worse or unknown.[124] However, the lack of placebo controls and the fact that participants were injected with different injection protocols complicates interpretation.[124]

The two medications with the most favourable benefit-to-harm ratio in preventive treatment against migraine, betablockers and angiotensin II receptor antagonists, are unfortunately poorly studied or not studied at all.[23,107]

2 Aims of the thesis

The overall aim of the thesis was to study whether headache attributed to injury to the head is a unique disease entity separate from the most common headache disorders.

2.1 Paper I:

The main aim of the first paper was to investigate whether the prevalence of headache was higher among persons previously exposed to head injury compared to uninjured controls and whether this was influenced by injury severity. A second aim was to investigate whether the prevalence of any headache subtype was more frequent among persons previously exposed to head injury. Our third aim was to identify potential predictors of headache in the head injury group.

2.2 Paper II:

The primary aim of the second paper was to analyse headache data for those who participated in both the second and third waves of the HUNT Study, evaluating the impact on new onset headache or exacerbation of headache due to head injuries in a population with known pre-injury headache status, taking into account the head injury severity.

2.3 Paper III:

The main aim of the third paper was to explore if patients with MTBI had an increase in headache suffering the first 3 months post-injury and 3-12 months post-injury compared to a control group with minor orthopaedic injuries and a community control group. A second aim was to study predictors of new headache or exacerbation of previously reported headache in the MTBI group.

3 Materials and methods

We performed three studies, each of which is described in a separate paper. The studies presented in Papers I and II were based on the same cohort, but with different selection of participants.

3.1 Study designs

3.1.1 Papers I and II

These studies were historical cohort studies. Data from hospital records on exposure to head injury during the period 1988-2008 were assembled in 2012-2013 and linked to two waves of a large epidemiological survey, performed in 1995-1997 and 2006-2008, with validated data on the occurrence of headache. Participants without hospital records on head injury were used as control groups.

3.1.2 Paper III

This study was a population-based, controlled, prospective cohort study that consisted of three study groups: one group exposed to MTBI, one group of controls with minor orthopaedic injuries and no head injury, and one group of community controls.

3.2 Study populations

3.2.1 The Nord-Trøndelag Health Study (HUNT) (Papers I and II)

The Nord-Trøndelag health study (HUNT1, 2 and 3) is a longitudinal cohort study inviting all adult inhabitants of the Nord-Trøndelag county in Norway to participate. In HUNT2 and 3, all residents from age 13 were invited to participate in Young-HUNT (13-19 years) or HUNT (≥ 20 years). HUNT2 was performed during 1995 to 1997, and HUNT3 during 2006 to 2008. All participants filled out two forms called questionnaire one (Q1) and a questionnaire two (Q2). The two questionnaires included more than 200 health-related items. Q2 included, along with several other questions, 13 headache questions in HUNT2 and 14 headache questions in HUNT3.

In our studies we used information from Q1 and Q2 in HUNT2 and 3. The exposed group in Paper I consisted of persons who had both been hospitalized in the region due to a head injury between 1988 and HUNT3 and had answered the headache questions in the HUNT3 questionnaire. The exposed group in Paper II consisted of persons who had both been hospitalized in the region due to a head injury between HUNT2 and HUNT3 and had answered the headache questions in the HUNT2 questionnaire as well as the HUNT3 questionnaire. In both papers, the control groups consisted of participants who had answered the same questionnaires as the exposed group, but not been hospitalized due to a head injury.

3.2.2 The Trondheim MTBI follow-up study (Paper III)

The Trondheim MTBI follow-up study consisted of three study groups: one group exposed to MTBI, one group of controls with minor orthopaedic injuries and no head injury (trauma controls) and one group of community controls. The MTBI group and the trauma controls were recruited from two emergency departments (ED) in Trondheim, Norway: St. Olav's Hospital (Trondheim University Hospital), a regional Level-1 trauma centre and Trondheim Municipal Emergency clinic (out-patients only) with a catchment area of 229 000 inhabitants. The community control group were recruited from the same catchment area and matched with regard to age, sex and education. The trauma control group were matched with regard to age and sex.

3.3 Procedures for inclusion and data collection

3.3.1 Inclusion of participants in Papers I and II

Inhabitants in Nord-Trøndelag who had answered the headache screening question in HUNT3 and also been hospitalized due to a head injury during the period 1988-2008 were identified in 2012 by a computer-based search. The national 11-digit identification number of all patients who had received one or more diagnoses related to head injury at the hospitals in Nord-Trøndelag (i.e. Levanger and Namsos) or the nearest university hospital (St. Olav's Hospital in Trondheim, Sør-Trøndelag) during 1988-2008 was registered. From this list, a data manager at the HUNT Research Centre identified all individuals who had answered the headache-screening question in HUNT3. Initially, all participants with head injuries who had received diagnostic codes from the International Classification of Diseases 9 (ICD-9) and 10 (ICD-10) referring to trauma to the body above the neck were included (Tables 3.1 and 3.2). Participants with diagnostic codes without assumed impact on brain function were later removed, and the final selection was done by search for the diagnoses printed in bold in Table 3.1 and 3.2.

Table 3-1 Relevant ICD-9 codes

800	**Fracture of vault of skull**
801	**Fracture of base of skull**
802	Fracture of face bones
803	**Other and unqualified skull fractures**
804	**Multiple fractures involving skull or face with other bones**
830	Dislocation of jaw
850	**Concussion**
851	**Cerebral laceration and contusion**
852	**Subarachnoid, subdural, and extradural haemorrhage, following injury**
853	**Other and unspecified intracranial haemorrhage, following injury**
854	**Intracranial injury of other and unspecified nature**
870	Open wound of ocular adnexa
871	Open wound of eyeball
872	Open wound of ear
873	Other open wound of head
910	Superficial injury of face, neck, and scalp except eye
918	Superficial injury of eye and adnexa
920	**Contusion of face, scalp and, neck, except eye(s)**
921	Contusion of eye and adnexa
925	**Crushing injury of face, scalp and, neck**
950	Injury to optic nerve and pathways
951	Injury to other cranial nerves

Bold = diagnostic codes with assumed influence on brain function

Table 3-2 Relevant ICD-10 codes

S00	Superficial injury of head
S01	Open wound of head
S02	**Fracture of skull and facial bones[1]**
S03	Dislocation, sprain and strain of joints and ligaments of head
S04	Injury of cranial nerves
S05	Injury of eye and orbit
S06	**Intracranial injury (includes concussion and cerebral contusion)**
S07	**Crushing injury of head (includes face)[2]**
S08	Traumatic amputation of part of head
S09	Other and unspecified injuries of head
T00.0	Superficial injuries involving head with neck
T01.0	Open wound involving head with neck
T02.0	**Fractures involving head with neck**
T03.0	**Dislocations, sprains and strains involving head with neck**
T04.0	**Crushing injuries involving head with neck**
T06.0	**Injuries of brain and cranial nerves with injuries of neck nerves/spinal cord**

Bold = diagnostic codes with assumed influence on brain function.[1] Only the subcategories S02.1, S02.7 and S02.9 were included. [2] Only the subcategories S07.1 and S07.9 were included.

Exclusion criteria were chronic subdural haematoma, no contact with the hospital in the first 48 hours after injury, and no matching information about trauma, or lack of signs and symptoms of head injury noted in the hospital record.

3.3.2 Head injury data collection in Papers I and II

Details regarding the head injuries were systematically collected. This was performed by two medical students (LHN and TP) and an experienced research nurse (GGB) in close dialogue with a neurologist with expertise in epidemiology and headache (ML) and a neurosurgeon with expertise in head injury (AV). All available information in the medical journals were scrutinized (physicians' notes, nursing records, referral letters, ambulance and air ambulance forms, other standardized forms in the records (e.g. monitoring form for patients with concussion of the brain) and discharge summaries). A total of 38 variables were recorded for each head injury (Supplementary Table 1). If the same individual had more than one head injury, up to three head injuries were recorded in chronological order starting with the most recent. We recorded any CT, MRI or X-ray imaging of the head performed because of the head injury within 3 months after the

injury. Clear clinical signs of cranial fractures (hemotympanum, bleeding that was clearly from the auditory canal and leakage of cerebrospinal fluid) were regarded as cranial fractures even without imaging evidence.

The head injuries were classified both according to HISS,[102] and ICHD-3 beta.[33] Since medical records often contain insufficient information to do this,[108] we applied the terms "*most likely*" or "*most likely not"* in some categories (Supplementary table 1). For HISS to comply with the terminology of the ICHD, we chose *not* to subdivide into moderate, severe and critical head injuries, but instead to use the combined term "moderate or severe head injury".

3.3.3 Headache questions in HUNT2 and HUNT3

Both the HUNT2 and HUNT3 questionnaires included the screening question "*Have you suffered from headache during the last 12 months*?". Individuals who answered "*yes*" were asked to answer the subsequent twelve (HUNT2) or thirteen (HUNT3) headache questions regarding how their headaches usually were regarding pain intensity, attack duration, and accompanying symptoms (Supplementary figures 1 and 2). The headache questions in HUNT2 were mainly designed to determine whether the person suffered from headache or not, and whether he or she fulfilled the migraine criteria of the International Headache Society (IHS)[31]; in HUNT3 the questionnaire enabled classification of definite migraine, probable migraine and tension-type headache (TTH), according to the ICHD-2 criteria[32]. Regarding duration of the attack, the participants were not explicitly instructed to report the duration of untreated attacks, because some individuals always use attack medication for their headaches.

The validity of these questionnaire-based diagnoses has been reported previously.[28,29] (Tables 3.4 and 3.5) A personal interview by a neurologist was used as the gold standard.

Table 3-3 Overview of the validity of the headache entities in HUNT2

	Sensitivity	Specificity	Kappa-values (95% CI)
Headache suffering	85%	83%	0.57 (0.41-0.73)
Migraine	69%	89%	0.59 (0.47-0.71)
Non-migrainous headache	61%	81%	0.43 (0.29-0.57)

Table 3-4 Overview of the validity of the headache entities in HUNT3

	Sensitivity	Specificity	Kappa-values (95% CI)
Headache suffering	88%	86%	0.70 (0.61-0.79)
Migraine	51%	95%	0.50 (0.32-0.68)
TTH	96%	69%	0.44 (0.30-0.58)
CDH	69%	99%	0.75 (0.56-0.94)
MOH	75%	100%	0.75 (0.30-1.00)

TTH = Tension-type headache, CDH = Chronic daily headache (headache occurring on ≥15 days per month), MOH = Medication overuse headache

3.3.3.1 Headache categories in Paper I

In Paper I, the headache questionnaire in HUNT3 was used to classify migraine and TTH, according to the ICHD-2 criteria.[32] The participants were also asked to state the consumption of over-the-counter (OTC) drugs for headache or musculoskeletal pain during the last month. This enabled a conservative diagnosis of medication overuse headache (MOH). Participants fulfilling both TTH and probable migraine criteria were classified as TTH. Since the participants were not specifically asked about the duration of untreated headache attacks, the ICHD-2 criteria for migraine were modified so that also duration of less than 4 hours was accepted. Chronic daily headache (CDH) was defined as headache occurring on ≥15 days per month. Medication overuse was defined as OTC-medication use for headache or pain in muscles and joints ≥4 days per week during the last month, and MOH was defined as CDH with medication overuse.

3.3.3.2 Headache categories in Paper II

In Paper II, the answers to the screening question "*Have you suffered from headache during the last 12 months*?" in both HUNT2 and HUNT3 were used to categorize the responders into four mutually exclusive groups with regard to headache suffering at the two time periods: Stable non-sufferers (headache-free in both studies), past headache sufferers (headache in HUNT2 but not in HUNT3), stable headache sufferers (headache in both studies) and new headache sufferers (headache in HUNT3, but not in HUNT2).

Participants answering "yes" to the headache screening question also reported the frequency of the headache. This enabled categorization of the headache sufferers in both surveys into three mutually exclusive groups: less frequent headache (in HUNT3 compared to HUNT2), stable headache frequency (same headache frequency in HUNT3 as in HUNT2), more frequent headache (in HUNT3 compared to HUNT2). Alternatives available for the headache frequency question were <7, 7-14 and >14 days/month.

To examine exacerbation or improvement of headache status between HUNT2 and HUNT3 we merged the frequency variable with the screening question so that each participant could be categorized into one of the following four groups: no headache suffering, headache suffering <7 days/month, headache suffering 7-14 days/month, headache suffering >14 days/month. Exacerbation of headache was defined as new onset of headache or increased frequency of previously reported headache. Improvement was defined as absence of or decrease in frequency of previously reported headache. Stable headache frequency was defined as headache suffering in both surveys with the same headache frequency in both.

Pre-existing headache was classified into two mutually exclusive groups: migraine and non-migrainous headache.

3.3.4 Inclusion of participants in Paper III

The inclusion period was April 2014 - December 2015 for the MTBI group and June 2014-December 2017 for the controls. Inclusion criteria for the MTBI group were having sustained MTBI and age 16-59 years. A recent definition of TBI, defining TBI as "an alteration in brain function, or other evidence of brain pathology, caused by an external force", was applied.[76] Patients were available for inclusion if they had experienced a physical trauma to the head or high energy trauma, and reported either witnessed LOC or confusion, self-reported amnesia for the event or the time period after the event, or traumatic brain lesions on CT.

TBI was categorized as mild according to the WHO criteria: GCS score 13-15 at presentation, and either LOC <30 minutes, confusion, or PTA <24 hours.[10] To ensure that self-reported amnesia was a result of MTBI and not intoxication, only patients who had been observed as fully conscious prior to the injury by witnesses accompanying them, or who reported complete memory for events immediately prior to the injury, were considered to have an MTBI.

Exclusion criteria in the Trondheim MTBI follow-up study were non-residency in Norway or non-fluency in the Norwegian language, ongoing, severe psychiatric disease, severe somatic disease or drug abuse that would complicate follow-up, history of complicated mild, moderate or severe TBI, other neurological conditions with brain pathology visible on imaging, known cognitive deficits, presentation >48 h after the

initial trauma, and other concurrent major trauma, such as spinal cord injury, severe fractures or internal injuries.

Inclusion criteria for trauma controls were fractures or symptoms from soft tissue injuries lasting ≥48 hours. Exclusion criteria were as for patients with MTBI; also excluded were head or neck injury, multitrauma, and trauma to dominant upper extremity.

3.3.5 Head injury data collection in Paper III

Information regarding the injury resulting in an MTBI and clinical symptoms at the ED was collected through medical records and by interview of the participants within two weeks of the injury. Previous MTBI was defined as having sustained one or more head injuries fulfilling diagnostic criteria for MTBI. The clinical radiology report was used to classify CT findings into intracranial findings and cranial fractures. An MRI examination was performed only if the patient lived within a one-hour drive, there was a time slot for MRI available within 72 hours and the patient consented to MRI. Intracranial pathology and cranial fractures on MRI or CT were dichotomised into "pathological imaging findings on CT or MRI" (yes/no).

3.3.6 Headache data collection in Paper III

Information regarding the participants´ headache status was collected through self-administered questionnaires, very similar to the questionnaire used in HUNT3, at three points in time (Supplementary figures 3-5). In the questionnaire at baseline the participants were asked about headache suffering the last year (i.e. baseline headache status). MTBI patients and trauma controls were asked to report headache the last year preinjury and community controls were asked to report headache the last year prior to administration of the first questionnaire. The participants answered the same headache questions after 3 and 12 months and were then asked to report headache the previous 3 and 9 months, respectively (Figure 3.1). Participants who answered ''yes'' to the first screening question ''Have you suffered from headache during the last year/last 3 months/last 9 months?'' answered the subsequent headache questions that enabled classification into definite migraine, probable migraine and TTH according to the ICHD-3 criteria[34]. Participants answering "no" to the headache screening question were considered non-sufferers. Headache sufferers were classified with regard to headache frequency and each participant was categorized into one of the following four groups: no

headache suffering, headache suffering <7 days/month, headache suffering 7-14 days/month, headache suffering >14 days/month. To be able to examine predictors for new headache or exacerbation of previously reported headache from baseline to the first 3 months post-injury (acute HAIH) and from baseline to 3-12 months post-injury (persistent HAIH) respectively, we defined *exacerbation of headache* as new onset of headache or increased frequency of previously reported headache the first 3 months post-injury or 3-12 months post-injury.

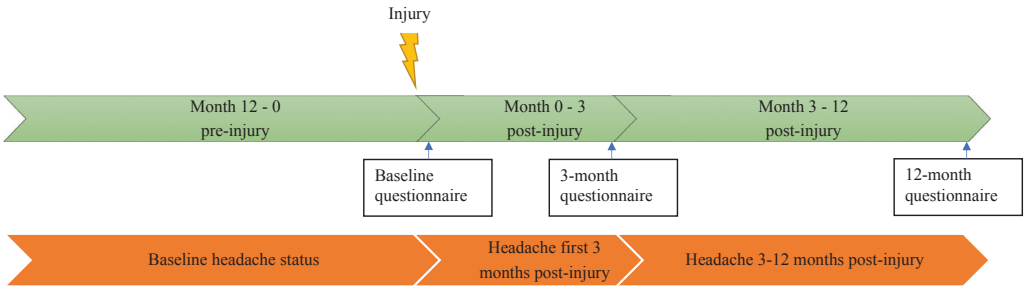

Figure 3.1 Timeline illustrating the time periods covered in each questionnaire

Baseline questionnaire: Headache suffering last 12 months prior to injury (MTBI and trauma controls) or first questionnaire (community controls). 3-month questionnaire: Headache suffering the first 3 months post-injury. 12-month questionnaire: Headache suffering 3-12 months post-injury.

3.4 Statistical analyses

Demographic data for all participant groups in all three papers are presented as follows. Continuous data are presented as means and standard deviations, while categorical data are presented as frequencies and percentages. P-values <0.05 were considered statistically significant.

3.4.1 Paper I

In multivariate analyses, using binary logistic regression, we estimated the odds ratios (OR) with 95% CI for the association between head injury and its subcategories and each category of headache. Head injuries were also stratified on the basis of when they occurred (the 50% most recent, i.e. ≤10 years before interview, and the 50% earliest head injuries, i.e. >10 years before interview). Persons not suffering from headache were used as reference category. We initially adjusted for age (continuous variable) and sex, and subsequently for other potential confounding factors identified by others (e.g.

smoking (yes/no), body mass index (BMI, continuous variable), and total Hospital Anxiety and Depression Scale (HADS) score (categorized from continuous variable into three categories with score boundaries ≤16, 17–21 and ≥22). Furthermore, to adjust for socioeconomic status, we included information on occupation (ten categories) and reclassified the subjects into an approximation of the international social class schema by Erikson, Goldthorpe and Portocarero (EGP).[20,54] The participants were classified into three categories: high social class (EGP I-II), medium social class (EGP III-IV) and lower social class (EGP V-VII).

Covariates that did not change the estimated ORs by at least 0.05 separately or together were excluded from the final model. This was the case for smoking and BMI. Subjects with incomplete HADS data variable were nevertheless included in all analyses, with the HADS score categorized as missing, to reduce the impact of response bias. In all analyses, two-tailed p-values were calculated.

3.4.2 Paper II

In multivariate analyses, using multinomial logistic regression, we first examined the association between head injury and relative headache status in HUNT3 versus HUNT2 with regard only to suffering from headache (yes/no). Then we examined the association between head injury and relative headache status in HUNT3 versus HUNT2 with regard both to suffering from headache and change in headache frequency. The results are presented as odds ratios with 95% confidence intervals. Stable non-sufferers were used as reference category. The associations were investigated both with head injury as a binary variable (yes/no) and with head injury in four categories according to head injury severity (no head injury/minimal/mild/moderate head injury).

In the multivariate analyses we initially adjusted for age and sex. Subsequently, we also added the following potential confounding factors retrieved from the HUNT2 dataset: duration of education (≤9, 10-12 and ≥13 years) as proxy for socioeconomic status, daily smoking (yes/no), total HADS score (categorized from a continuous variable into three categories with score ≤16, 17-21 and ≥22) and CAGE score (0 or ≥1). In the logistic regression analyses, missing data were handled by listwise deletion. Linearity of the continuous variables with respect to the logit of the dependent variable was assessed via the Box-Tidwell procedure.[6] The continuous variable age was found to fail the assumption of linearity and was split into categories with 10 year intervals. We investigated potential interactions between all covariates and head injury by including

the product of the two variables into the multinomial logistic regression analyses. The interaction coefficients were tested using Wald statistics, with p-values less than 0.05 considered statistically significant. Because headache disorders in general are highly dependent on sex,[63] separate analyses after stratifying for sex are common in research concerning headache. Consequently, we chose to also perform separate analyses after stratifying for sex. No formal adjustment for multiple testing was made.

3.4.3 Paper III

We used generalized linear mixed model (GLMM) to compare the development of headache status regarding headache suffering or no headache suffering between the three groups (MTBI, community controls and trauma controls) over time (baseline, first 3 months post-injury and 3-12 months post-injury). To control for known confounders, the model included age, sex, lower secondary school grades as proxy for socioeconomic status and alcohol use as covariates. A random, subject-specific intercept was included to account for within-subject dependencies. Missing outcome variables for subjects with at least one observation on outcome were handled by the model, while missing explanatory variables were handled by listwise deletion.

We used multivariate logistic regression to identify predictors for exacerbation of headache within the first 3 months post-injury (acute HAIH) (among the participants answering both the baseline and 3-month questionnaires) and exacerbation of headache 3-12 months post-injury (persistent HAIH) (among the participants answering both the baseline and 12-month questionnaires) for the MTBI participants. We examined age (continuous variable), sex (male/female), lower secondary school grades as proxy for socioeconomic status (continuous variable), GCS score (13-14/15), PTA (1-24 hours/<1 hour), previous MTBI (yes/no), pathological imaging findings (fracture or intracranial pathology) on CT or MRI (yes/no) and influenced by alcohol at time of injury (clinically assessed or self-reported) (yes/no) as potential predictors. In addition, we performed a separate analysis examining acute HAIH (yes/no) as predictor for persistent HAIH, including the previously mentioned predictors as covariates. Missing data were handled by listwise deletion.

Linearity of age as a continuous variable with respect to the logit of the probability of headache (yes/no) was assessed via the Box-Tidwell procedure. Based on this assessment, age was found to be linearly related to the logit of the dependent variable.

The results for both analyses are presented as odds ratios (OR) with 95% confidence intervals (CI).

Statistical analyses were performed with IBM SPSS Statistics versions 21-25 in all analyses, except for the GLMM-analysis in Paper III, where we used Stata/MP 15.

3.5 Ethical approval

All three studies were approved by the Regional Committee for Medical and Health Research Ethics and by the HUNT Research Centre. In the third study (Paper III), participants, or parents of participants below age 18, gave informed consent.

4 Summary of results

4.1 Participants and classification of the head injuries

4.1.1 Paper I and II

There were 25,760 registered hospital-referred head injuries at Levanger and Namsos hospitals and 119,402 at St. Olav's Hospital in Trondheim between 1988 and 2008. Linkage of the patients' national identification numbers to the HUNT database revealed that 2,889 of the persons with hospital-referred head injuries had answered the headache questions in HUNT3. Of them, 1,183 had a head injury with a diagnostic code reflecting assumed influence of brain function. Among these, 66 experienced their head injury after the HUNT3 survey and were thus not eligible, and 177 were excluded with regard to the exclusion criteria. The total population in paper I was thus 940 persons with head injuries. Of these, 55 had more than one head injury adding up to a total of 1,001 head injuries. Mean age at (first) injury in the head injury group was 39.9 years (SD 19.6 years), mean age at participation in HUNT3 was 50.6 years (SD 17.9), and 54.8% were male. In the control group mean age at participation in HUNT3 was 54.2 years (SD 15.6), and 43.8% were male. 11.0% of the head injuries were minimal, 68.0% were mild, 10.8% were moderate, 0.9% were severe and 4.5% were unclassifiable. The most common injury mechanism was falling (46.6%), followed by traffic accidents (including bicycle accidents) (33.3%) and assault (6.6%). A CT scan was performed on 40%, an MRI on 1% and a plain X-ray of the head on 11% of the patients. The scans revealed traumatic pathology in 11% of all patients in the cohort. In total, 6.5% (n = 61) had intracranial pathology, 7.7% of all patients had cranial fractures (revealed either by

imaging or clinical findings), and 3.3% had both cranial fracture and intracranial pathology.

In paper II, only participants who answered the headache screening question in both HUNT2 and HUNT3 were of interest for analyses. Of these, a total of 294 participants had been hospitalized due to a head injury during the 11-year time period between HUNT2 and HUNT3. The remaining 25,662 individuals who had participated in both studies were not hospitalized for head injury during this period. Mean age at (first) injury in the head injury group was 53.8 years (SD 15.2 years), mean age at participation in HUNT3 was 59.6 years (SD 14.7), and 53.5% were male. In the control group mean age at participation in HUNT3 was 58.5 years (SD 13.1) and 43.0% were male. Among the 294 individuals with head injuries, 11 experienced two head injuries, adding up to a total of 305 incidents. Considering only the first head injury (of those with more than one), 11.9% of the head injuries were minimal, 71.8% were mild, 10.9% were moderate and 5.4% were unclassifiable. There were no severe head injuries. The most common injury mechanism was falling (55.1%), followed by traffic accidents (including bicycle accidents) (28.6%) and assault (1.7%). A CT scan was performed in 56.4%, an MRI in 1.0% and a plain X-ray of the head in 3.6% of the cases. The scans revealed traumatic pathology in 16.0%. In total, 9.2% of all patients had intracranial pathology. 9.9% had cranial fractures (revealed either by imaging or clinical findings), and 5.1% had both cranial fracture and intracranial pathology.

4.1.2 Paper III

The MTBI group consisted of 378 participants. The control groups consisted of 82 trauma controls with minor orthopaedic injury and 83 community controls. Mean age in the MTBI group was 31.2 (SD 13.0 years) and 65.3% were male. The control groups were matched with the MTBI group on age and sex. Only 31.2% of the MTBI participants were admitted to hospital; 51.7% of these were observed <24 hours. The most common injury mechanism was falling (35.7%) followed by assault (17.2%), bicycle accidents (15.3%), sport accidents (14.3%) and motor vehicle accidents (11.4%). In total 333 (88.1%) of the MTBI group had either a CT or an MRI examination. In total, 88.1% of the MTBI group had either a CT or an MRI examination. Traumatic pathology was revealed in 9.8% of the MTBI participants. Intracranial pathology was revealed in 8.5%, 4.2% had cranial fractures and 2.9% had both cranial fracture and intracranial pathology.

4.2 Association between head injury and headache

4.2.1 Paper I

In multivariate analyses, adjusting for age, gender, anxiety, depression and socioeconomic status, individuals who had been hospitalized due to a head injury were more likely to have any headache (OR 1.19, 95% CI 1.04-1.37), migraine (OR 1.47, 95% CI 1.20-1.79), chronic daily headache (OR 1.87, 95% CI 1.37-2.61), and medication overuse headache (OR 2.10, 95% CI 1.34-3.28) compared to controls. When doing a separate analysis with head injury in categories according to head injury severity we observed an even greater odds of headache for individuals with mild head injury than when investigating all individuals exposed to head injury regardless of severity: any headache (OR 1.28, 95% CI 1.08-1.52), migraine (OR 1.66, 95% CI 1.31-2.09), chronic daily headache (OR 2.33, 95% CI 1.61-3.37), and medication overuse headache (OR 2.55, 95% CI 1.55-4.19). Individuals with mild head injury also were more likely to have CDH, even after removing the participants with medication overuse from the analysis (OR 2.01, 95% CI 1.16-3.49). Individuals exposed to a moderate or severe head injury did not have increased odds of headache compared to controls. Using ICHD-3 beta for classification of head injury severity in our analysis resulted largely in the same conclusions as using HISS.

No significant relationship was found between head injury and TTH.

Subjects having more than one head injury showed an even greater odds of headache compared to controls than when investigating all individuals exposed to head injury without specification of iteration. (Any headache OR 2.46, 95% CI 1.38-4.40, Migraine OR 3.52, 95% CI 1.70-7.29)

4.2.2 Paper II

Individuals who had been hospitalized due to a head injury were more likely to have stable headache suffering (OR 1.55, 95% CI 1.12-2.14) and exacerbation of headache status (OR 1.52, 95% CI 1.02-2.25) compared to controls. When doing a separate analysis with head injury in categories according to head injury severity, we saw that individuals with mild head injury were more likely to have new onset of headache (OR 1.74, 95% CI 1.05-2.87) compared to controls. We also observed an even greater odds of stable headache (OR 1.70, 95 CI 1.15-2.50) and exacerbation of headache status (OR

1.93, 95% CI 1.24-3.02) for individuals with mild head injury than when investigating all individuals exposed to head injury regardless of severity.

There was no significant relationship between moderate head injury and any of the headache trajectories. There were no significant associations between head injury and past headache suffering or improvement of headache status.

4.2.3 Paper III

In the MTBI group, the odds of headache increased significantly from baseline to the first 3 months post-injury (OR 8.61, 95% CI 4.90-15.13) and from baseline to 3-12 months post-injury (OR 3.72, 95% CI 2.19-6.31). There was furthermore a significant decrease in odds of headache from the first 3 months post-injury to the next 9 months (OR 0.43, 95% CI 0.25-0.73) in the MTBI group. In the trauma control group, the OR indicated an increase in odds from baseline to 3-12 months post-injury (OR 2.17, 95% CI 0.81-5.81), but this was not statistically significant. In the community control group there was a significant increase in the odds of headache from baseline to 3-12 months post-injury (OR 3.07, 95% CI 1.23-7.65).

The development in odds of headache over time differed significantly between the groups (overall p=0.035 for the interaction between time and group). Figure 4.1 shows the trajectories of log odds of headache in the MTBI group and the two control groups. The increase in odds of headache from baseline to the first 3 months post-injury was significantly larger for the MTBI group than for the community controls (ratio of OR 3.56, 95% CI 1.09-11.66), and the trauma controls (ratio of OR 4.33, 95% CI 1.50-12.47). However, the odds ratios of headache from baseline to 3-12 months post-injury did not differ between the groups.

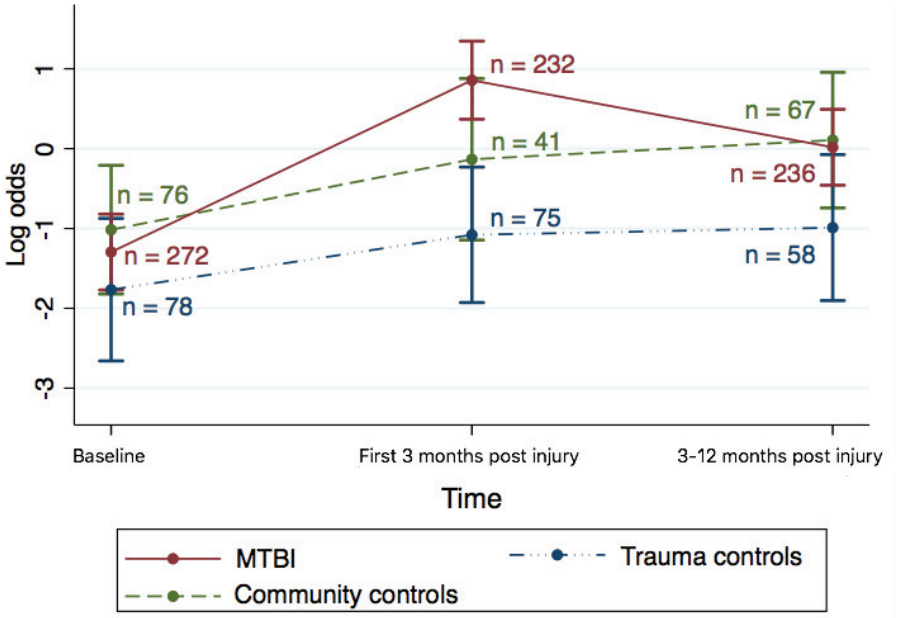

Figure 4.1 (Paper III) Estimated values of log odds with 95% CI for headache pre-injury, the first 3 months post-injury and 3-12 months post-injury for the MTBI group and two control groups.

Baseline: Headache suffering last 12 months prior to injury (MTBI and trauma controls) or first questionnaire (community controls). 3-month questionnaire: Headache suffering the first 3 months post-injury. 12-month questionnaire: Headache suffering 3-12 months post-injury.

4.3 Classification of HAIH into primary headaches

4.3.1 Paper I

When classifying the headaches according to criteria for primary headache disorders, the higher occurrence of headache among individuals exposed to head injury was only evident for migraine (any head injury and migraine (OR 1.47, 95% CI 1.20-1.79)), Mild head injury and migraine (OR 1.66, 95% CI 1.31-2.09)) with the exception of TTH in the most recent injuries (≤10 years before interview) (OR 1.36, 95% CI 1.06-1.74).

4.3.2 Paper III

Figure 4.2 shows the share of participants in the MTBI group who developed exacerbation of headache status, including headache subgroup.

When classifying the HAIH as primary headaches according to ICHD-3, migraine was the most common phenotype. The first 3 months post-injury 47.9% of the subjects reported exacerbation of headache. Of these, 49.5% reported a migraine headache and 8.6% reported MOH. 3-12 months post-injury, 35.7% of the subjects reported exacerbation of headache compared to baseline. Of these, 57.9% reported a migraine headache and 9.2% reported MOH.

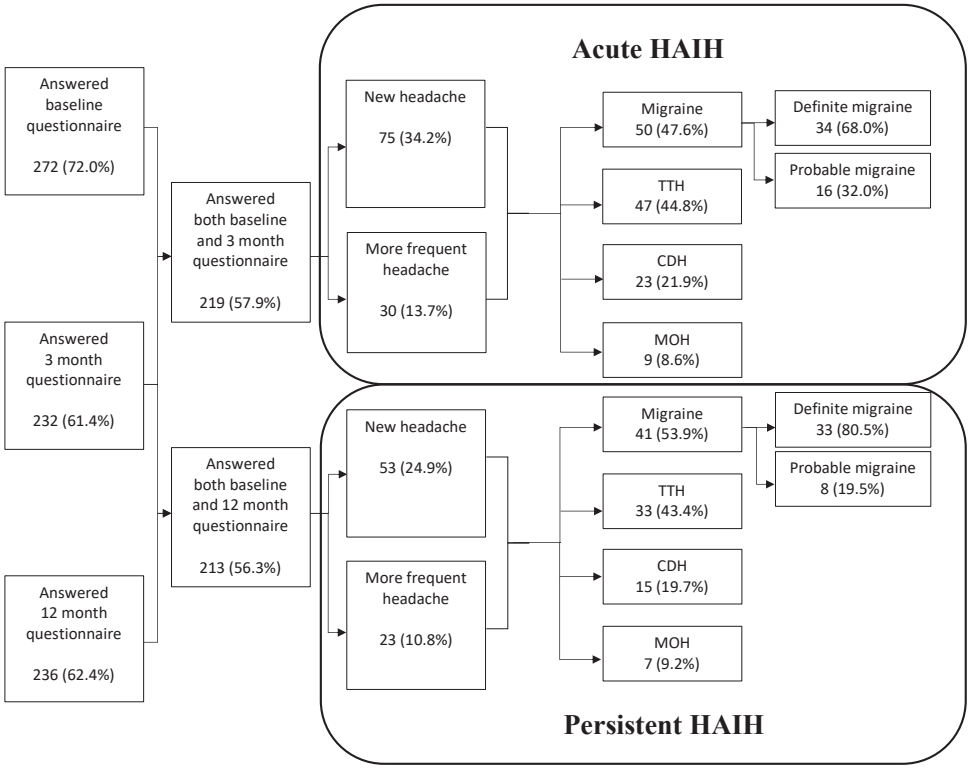

Figure 4.2 (Paper III) The share of participants in the MTBI group who developed new headache or exacerbation of pre-existing headache including headache subgroup.

CDH= Chronic daily headache, MOH= Medication overuse headache, TTH= Tension-type headache.

4.4 Predictors of headache following head injury

4.4.1 Paper I

Previous head injuries were significantly associated with any headache only if they had been accompanied by headache during the hospital stay (OR 1.36, 95% CI 1.15-1.62), nausea at admission (OR 1.25, 95% CI 1.04-1.50) or dizziness at admission (OR 1.35, 95% CI 1.04-1.75). There was no significant association between any headache and acute alteration in mental state at the scene or at admission, cranial fractures or traumatic intracranial pathology.

4.4.2 Paper III

Female sex (OR 2.52, 95% CI 1.35-4.72) and pathological imaging findings on CT or MRI (OR 2.88, 95% CI 1.16-7.15) were significant positive predictors for acute HAIH, but this was no longer the case for persistent HAIH for either of them. Significant positive predictors for persistent HAIH were prior MTBI, (OR 2.89, 95% CI 1.28-6.53) and being injured under the influence of alcohol (OR 2.06, 95% CI 1.04-4.09). Age, socioeconomic status, duration of PTA and GCS score were not significant predictors of acute or persistent HAIH. However, the OR for persistent HAIH among those with PTA >1 hour was 0.49. (95% CI 0.22-1.13). In a follow-up analysis, we also included "having acute HAIH" in the regression analyses. This variable was highly significantly associated with persistent HAIH (OR 5.63, 95% CI 2.54-12.50).

5 Discussion

5.1 Methodological considerations

The objective of an epidemiological study is to obtain a *precise* and *valid* estimate of the frequency of a disease or of the effect of an exposure on the occurrence of a disease in the study population.[49]

5.1.1 Precision

In this thesis, we attempted to estimate the association between exposure to head injury, and headache as an outcome. Because of random, unexplained variation in the data (random error), the estimated variation will always have a degree of uncertainty. To present the result of our study we have used odds ratios as *point estimates*. To indicate the *precision* of the point estimate, it is common to use a *confidence interval,* which is a range of values around the point estimate. A wide confidence interval indicates low precision, and a narrow interval indicates high precision.[49] A large sample size will have little random error in the estimation and thus high precision, while a small sample size will have less precision. A given confidence interval is tied to an arbitrarily set level of confidence, commonly 95%, as we have used in the papers presented in this thesis.[49] However, the defined level of confidence presumes that there is no systematic error (bias or confounding) in the study and the confidence interval should only be considered together with the validity of the study.

Another commonly reported statistical measure is the *p-value.* The p-value is usually calculated in relation to the null hypothesis, which states there is no relation between exposure and disease. If we assume that the null hypothesis is true, the p-value represents the probability of finding the observed association (or one even further from the null hypothesis).[49] The null hypothesis is rejected when the p-value is below a certain cut-off point, usually 5%.[49] P-values are presented in Paper I and Paper III.

In Papers I and II we had a very large sample size from the HUNT-studies. However, in our studies, the precision also depends on the exposure variable studied, i.e. head injuries. Especially in the analyses where we separated head injury in several categories according to head injury severity, some categories had only a few cases (e.g. moderate and severe head injury). This gives low statistical power, with a wide confidence interval around the point estimate, and the results are difficult to interpret. This was also the case in the analyses of some of the proposed predictors of headache following head injury in Paper I. Only 26 of the participants who had experienced a head injury with cranial fracture, and only 20 participants with a head injury with an intracranial traumatic lesion were included in the analyses. We had a similar situation in Paper III. In the analysis of predictors of exacerbation of headache, 29 persons with imaging findings were included in the analysis for acute HAIH and 28 were included in the analysis for persistent HAIH. The small sample sizes make it more likely that random error could have affected the result of the analyses. A small sample size and low statistical power increases the risk of failing to reject a false null hypothesis, also known as a Type-II error.[49] In our case, that would mean that we were at risk of failing to see an association between moderate or severe head injury and headache in Paper I and Paper II, and wrongly discard cranial fractures or intracranial traumatic lesions as predictors for headache in Paper I, or imaging findings on CT or MRI as a predictor for acute or persistent HAIH in Paper III.

5.1.2 Validity

Validity is the extent to which an estimate is well founded and likely corresponds accurately to the real world. The validity of the estimate for the study population is often called *internal validity* and most violations of internal validity can be classified into*, selection bias, misclassification (information) bias and confounding*. If one wishes to apply

the estimate for the study population on another population it is important to also consider the *external validity* of the estimate.[49]

5.1.2.1 Selection bias

When the subjects that are studied vary systematically from the ones not studied we have selection bias.[49] The reasons for these systematic differences between participants and non-participants in a study include both procedures to select subjects, and factors that influence study participation.[49]

All three studies in this thesis were population-based and selection bias due to sampling methods were mainly avoided. However, in the Trondheim MTBI follow-up study described in Paper III, the inclusion of controls was done on the basis of matching the control groups to the MTBI group with regard to age and sex for the trauma controls and age, sex and education for the community controls. The trauma controls were recruited at the same EDs as the MTBI group, but, in contrast to the MTBI group, not all patients with minor orthopaedic trauma during the inclusion period were requested to participate in the study. The community control group was recruited among students and employees at the hospital and among acquaintances of patients and researchers working with the study. Although they were matched with the MTBI group with regard to important confounders, it is possible that there are some systematic differences between the MTBI group and the control groups.

In Paper III, we recruited patients from both a trauma-centre and a general practitioner-run municipal outpatient-clinic.[99] In the studies described in Papers I and II, however, only hospitalized patients were included, and this could have resulted in a biased selection of more severe head injuries, making the sample less representative for all persons exposed to head injury in the region. However, the proportion of patients with head injury being admitted to a hospital after examination by health care providers was larger in the period of data collection than it is today.[35,36] This can mostly be attributed to increased availability of CT imaging and the implementation of guidelines for initial management of head injury in Norwegian hospitals.[43]

People suffering from headache are more likely to participate in headache studies because they have more personal interest in them. This can give rise to a form of selection bias called participation bias or interest-related bias.[106] Headache was not the

primary objective of either the HUNT studies or the Trondheim MTBI follow-up study. This makes selective participation due to headache unlikely.

The HUNT-studies have been thoroughly described by others. Krokstad, Langhammer and Holmen with colleagues have published descriptions of participants, non-participants and the relationship between these two groups:[48,55,59,103] Of a total of 93 898 persons eligible for participation in HUNT2, 69.5% participated and 78.8% of these responded to the headache questions. In HUNT3, 93 860 persons were eligible, 54.1% participated and 78.1% of these responded to the headache questions.[55] In total, 37 071 persons participated in both HUNT2 and HUNT3 and 70.7% of these responded to the headache questions. In both HUNT2 and HUNT3, more women than men participated, and the highest participation was in the middle aged and the elderly (50–79 years), with lower participation in the oldest (80+ years) and the youngest (<40 years).[55]

Shortly after HUNT2 a 2.5% random sample of non-attendants was selected for a non-participation study. The aim was to investigate the reasons why they did not attend.[48] In age group 20-44 the main reasons for not attending were lack of time or having moved out of the county. In the age group 45-69 the main reasons were: lack of time, had forgotten the invitation, or had no reason. In age group 70+ many reported having regular follow-up by a doctor or hospital and therefore did not need to attend a health survey. Some people (9.6%) could not attend because they were immobilized due to disease, and some (8.6%) reported that the health survey was unnecessary or that they were unwilling to participate. A few (4.1%) refused due to long waiting time at the screening site.[48]

After HUNT3 a comparison was performed between participants answering the main questionnaire in HUNT3 and respondents only answering a non-participation questionnaire, national registers and data from randomly selected general practices.[59] Non-participants had lower socioeconomic status, higher mortality and showed higher prevalence of several chronic diseases.[59] Among women, persons answering the non-participation questionnaire reported more headache and migraine suffering than participants in HUNT3. Among men, there was no significant difference.[59] The most important reasons for non-participation was lack of time or inconvenient session (50.7% in women and 56.6% in men).[59] About 10% reported that they had not received the invitation to HUNT3. For all age groups, 4.7% of women and 2.6% of men reported

being too ill to participate, while for the participants ≥ 80 years the proportion was 23.7% for women and 19.5% for men.[59] The sickest elderly, adults with serious social and economic problems, adults in the coastal region (who have somewhat worse health than others in the county), and adults with low socioeconomic status participated in HUNT3 to a lesser degree than others.[103] This selection bias is likely to result in a slight underestimation of the total morbidity in the population and an underestimation of the differences in health between socioeconomic groups in the population. The attendance among young adults was also lower than among middle aged. While the results should be representative of the vast majority of the population, they do not provide an accurate description of the health of the very sickest.[103]

Skandsen et al. have published a description of the participants and non-participants in the Trondheim MTBI follow-up study:[99] During the inclusion period, 624 persons exposed to MTBI presented to the study EDs and had a head CT. Of these, 164 (26%) met one of the exclusion criteria. The reasons for exclusion were medical conditions, including substance abuse (40%), presenting late (29%), non-fluency in Norwegian (28%) and having other major trauma (4%). The median age in this group was higher than the enrolled patients.[99] Of the remaining eligible MTBI patients, 160 were not enrolled (53 declined participation, 80 were not reached, 17 were never contacted and 10 did not participate due to unknown reasons). Compared to the participants, they were more likely to be female, more likely to have sustained injury by violence, were more often injured during the weekend, and were more often discharged from the ED.[99]

The exclusion criteria in the Trondheim MTBI follow-up study were designed to exclude only those impossible to follow up, or whose outcome would not be valid. In spite of this, a quarter of the potential participants had to be excluded. This demonstrates that all follow-up studies in patients with MTBI will suffer from some selection bias.[99] There were some differences between participants and eligible patients not enrolled, but these differences were small.[99] The response rates to the questionnaires were acceptable (Table 1, Paper III). We consider the results from the Trondheim MTBI follow-up study to be representative for the study population.

5.1.2.2 Information (misclassification) bias

Information bias is the bias caused by measurement errors in the information needed in the estimation of an effect.[49] For discrete variables, measurement error is usually called misclassification (i.e. the variable has been wrongly classified).

The limitations of recall (correctly remembering what happened when) are an important factor in the generation of information bias.[106] In Paper III, the participants were included in the study after their MTBI. In all studies with retrospective questions given after the head injury, assessment of pre-injury headache suffering may always be influenced by recall problems as participants might tend to trivialise headache before the head injury because they understand their headache as a consequence of their head injury. Such possible under-reporting of pre-injury headache could be the reason why several longitudinal studies report pre-injury headache prevalences far below the known headache prevalence in the general population.[101,105,119] This is especially a problem in studies without control groups. However, in Paper III we did an assessment of pre-injury headache suffering very shortly after the injury (within two weeks). The proportion reporting headache suffering during the last year prior to the head injury was similar in the MTBI group and the control groups. It was also very similar to the headache prevalence reported from the HUNT3 study, which used the same validated headache questionnaire as in Paper III[63]. This means that the study is at low risk of recall bias.

In Paper II, we had validated information about the headache status of the participants before the head injury, which enabled us to compare prevalence as well as frequency before and after the time of the head injuries and make comparisons with a non-exposed control group. This design eliminates recall bias, and this has, to my knowledge, not been possible in earlier studies of HAIH.

In all three papers, headache questionnaires were used to classify headache according to either the ICHD-3 beta[33] or ICHD-3 criteria[34]. However, the ICHD criteria were not designed for epidemiological enquiry. Their application requires personal interviews, and in some cases, examination by an experienced clinician, to make an exact diagnosis.[93,106] Therefore, we had to make modifications to the criteria to be able to classify the participants' headaches. Participants were not specifically asked about the duration of untreated headache attacks, because some individuals always use attack

medication for their headaches. Because of this, the ICHD-3 criteria for migraine were modified so that duration of less than four hours was accepted as well. Every participant with headache suffering was registered with only one headache diagnosis. In a study on the prevalence of headache in adolescents in the same study area as ours, the authors found that 9% of the adolescents, when interviewed about their headache, fulfilled criteria for more than one headache type.[53] They also found that there was a systematic underestimation of TTH among those with both TTH and migraine.[53] Because we registered only one headache diagnosis per participant, there could be underreporting of TTH in our study sample.

The screening question in the headache questionnaire in all three papers was: "*Have you suffered from headache during the last 12 months*?". When the participant is asked about *suffering* from headache and not having *experienced* headache, the prevalence will most likely be lower. However, asking about headache suffering will most likely ensure that those who have insignificant headache once in a while, will answer "no" to the screening question. That leaves only those who are actually affected by their headaches.

Chronic daily headache (CDH) was defined as headache occurring >14 days/month. CDH is not a specific diagnosis in ICHD-3, but is used to describe the headache frequency. In both Paper I and Paper III we included a diagnosis of medication overuse headache (MOH). In ICHD-3, MOH is defined as a headache occurring on >14 days/month in a patient with a pre-existing primary headache and developing as a consequence of regular overuse of acute or symptomatic *headache medication* for *more than three months*.[34] The headache questionnaire in HUNT did not include a question about medication use, but participants answered a question in the same questionnaire about over-the-counter (OTC) drugs during the last month. We did not have information about prescribed analgesics and triptans, or information about medication use previous to the last month. Thus, in Paper I, medication overuse was defined as OTC-medication use for headache or pains in muscles and joints ≥ 4 days per week during the last month. In Paper III, the questionnaire included a question about use of pain medication or acute migraine medication against headache during the last month. This diagnosis of medication overuse in Paper III thus includes use of prescribed analgesics and triptans, but as in Paper I, only for the last month. In both Paper I and Paper III, MOH was defined as CDH with medication overuse.

Because the diagnosis set by headache questionnaires deviates from the accepted criteria in ICHD, two validation studies of the headache questionnaires in HUNT2 and HUNT3 have been performed. In these studies, the questionnaire-based headache diagnoses were compared to diagnoses made in a clinical interview.[28,29] The results of these studies are described in *3.3.3 Headache questions in HUNT2 and HUNT3.* Because the headache questionnaires in HUNT have been found valid, the headache questionnaire in Paper III was designed very similar to the questionnaires used in HUNT (Supplementary figures 2-5). The bias caused by misclassification of headache diagnosis can either exaggerate or underestimate the true difference between headache groups in the analyses of association between head injury and the different subtypes of headache.

We were not able to determine if the onset of headache was within 7 days after head injury in any of the three papers. This is a criterion for classifying a headache as attributed to traumatic injury to the head, according to ICHD-3.[34] However, several studies have indicated that this criterion may be too strict.[38,68,70] Overly strict criteria can lead to an underestimation of the true incidence of HAIH.

In Paper I, we did an analysis on signs and symptoms during the hospital stay as predictors of headache in HUNT3. Information on the signs and symptoms were retrieved from the participants' medical records. Missing data may have led to overrepresentation of certain predictors because the physicians were more likely to make notes in the medical record of present signs and symptoms than absent ones. However, the proportion of data missing was low (Table 5 in Paper I).

5.1.2.3 Confounding

If we observe an association between an exposure (e.g. head injury) and an outcome (e.g. headache) that in reality is due to an external factor (i.e. a confounding factor), we have *confounding.* Confounding can lead to over- or underestimation of an effect or can even change the direction of an effect.[49] Confounding factors are associated with both the exposure and the outcome, but not caused by either. Confounding are usually dealt with in the statistical analyses of a study and this can be done either by stratifying the analyses on the confounding variables or including the confounding variables in a regression analysis.[49]

In this thesis, confounding has been addressed by including suspected confounders in regression analyses, in addition to one stratified analysis in Paper II. In all papers we had the possibility to evaluate a large number of confounders because both the HUNT-studies and the Trondheim MTBI follow-up study collected many demographic and health related variables on each participant. Included variables in each paper are described in *3.4 Statistical analyses.* We used clinical knowledge and available literature on associations between the potential confounding factor and headache and head injury to identify possible confounders. In Paper I, we excluded covariables from the final model that did not change the estimated ORs separately or together with more than 0.005. This was not done in Paper II and Paper III.

Although we had many available covariates, it is difficult to take all confounders into account. Residual confounding could be a problem in all three papers.

5.1.2.4 External validity

The external validity of estimations done in epidemiological studies describes how valid the estimate for the study population is on another population,[49] or in other words: the generalizability of the results. All three papers in this thesis are based on population-based studies and thus has the aim of finding estimates valid for the entire defined population. The discussion on participation rate and evaluation of non-participants in *5.1.2.1 Selection bias* is therefore applicable also here.

The population invited to the HUNT studies are inhabitants of Nord-Trøndelag county in Norway. Nord-Trøndelag consists of mainly rural areas with five small towns. The population is homogenous and has a level of education and income a little below the national average. However, mortality and health status is fairly representative of Norway.[59]

The catchment area for MTBI at Trondheim Municipal Emergency Clinic and St. Olavs Hospital is the city of Trondheim and four neighbouring municipal entities with a total of 229,000 residents, in addition to 18,000 students, who come from other areas in Norway.[99] As this is an area where most of the population resides in a university city, the population is influenced both by a high number of students, and by a somewhat higher level of education among the citizens than the national average.

Since factors related to low socioeconomic status have been found to be risk factors for mild traumatic brain injuries, results may not be generalized to the whole country in any of the papers.[83] The results of the two studies should, however, complement each other since both studies have participants with an education level on either side of the national average.

5.2 Appraisal of main findings

5.2.1 Association between head injury and headache

In Paper I we examined headache prevalence in the head injury group compared to controls after an average interval of 10 years following the head injury, and in Paper II after an average of 5 years following the head injury. In Paper III we examined both the first three months post-injury and 3-12 months post-injury.

In Paper I, we found that individuals with head injury were more likely to have any headache, migraine, CDH and MOH compared to controls. In Paper II, we had information about headache suffering before the injury and were able to investigate new headache suffering and exacerbation of previously reported headache. Individuals with head injury were more likely to have stable headache suffering and exacerbation of headache status compared to controls. Individuals with mild head injury were more likely to have new onset of headache compared to controls. In Paper III, the increase in odds of headache from baseline to the first 3 months post-injury was significantly larger for the MTBI group than for trauma controls and the community controls. However, the odds ratios of headache from baseline to 3-12 months post-injury did not differ between the groups. Thus, the first two papers suggest that HAIH is persistent over several years, while Paper III only finds evidence for acute HAIH. In Paper III we saw, somewhat surprisingly, that also the control groups had an increase in headache suffering from baseline to 3-12 months post-injury, but this was only statistically significant for community controls (Table 4, Paper III). This increase in odds of headache suffering in the control groups, seen together with the decrease in odds of headache suffering from the first 3 months post-injury to 3-12 months post-injury in the MTBI group could explain that the MTBI group did not differ from the control groups between baseline and 3-12 months post-injury. The increase in odds of headache suffering from baseline to 3-12 months post-injury in the control groups could have been caused by some of the biases introduced previously (i.e. selection bias or misclassification bias), but could also be a demonstration of the dynamic course in headache. In a study of a random sample of 5,000 adults selected from five general practices in the United Kingdom, the authors showed that 24% of respondents without recent headache (last 3 months) at baseline reported headache in at least one follow-up the following year[4]. This supports that

headache suffering is a dynamic disease in the general population and an increase in headache suffering could be observed also in persons not exposed to a head injury.

There are, to my knowledge, only two other controlled population-based studies on the association between head injury and headache, one with a historical cohort design, and one with a retrospective design. The first one, a Norwegian population-based historical cohort with an uninjured control group, found no association between previous head injury and headache 22 years after hospitalisation for head injury.[82] However, that study had low statistical power, since the sample-size was only 192, and the control group differed significantly from the exposed group with regard to several important confounders.[82] The second study, a retrospective study from the USA, studied the association between CDH and head or neck injury.[15] Cases with CDH and a comparison group with episodic headache were identified from the general population and asked about lifetime occurrence of head and neck injury. The authors found that CDH cases were more likely to have had a lifetime occurrence of head and neck injury than controls with episodic headache.[15] However, also this study had a small sample size, with only 187 cases.[15]

There are some non-population-based studies with control groups on the occurrence of HAIH, but most of them have short follow-up time and therefore do not include an assessment of persistent HAIH. To my knowledge, there are only two non-population based, controlled studies, with as long as 12 months follow-up. The first is a combined historic and prospective cohort from Lithuania.[105] The authors of this study showed that migraine occurred significantly more often in patients with MTBI than in patients with a minor orthopaedic trauma after 3 months, and headache diagnoses and headache frequency amongst patients with MTBI occurred in similar proportions as in the orthopaedic controls 12 months after the MTBI.[105]. These results are in line with our results in Paper III. In the study from Lithuania, however, the proportion of participants in the exposed group who reported headache the last year prior to the head injury were considerably lower than in the control group (44.2% vs. 71.9%).[105] This gives reason to suspect recall bias in the exposed group. The second study is a study from the USA where the authors compared new or worse post-traumatic symptoms, including headache, in patients exposed to TBI and a control group exposed to trauma without head injury.[18] The authors found that a significantly larger proportion of the TBI group

reported new or worse headache compared to the control group at both 1 month and 1 year following the injury.[18] However, in this study, they did not ask the participants specifically about pre-injury headache. The method for identifying that the headache suffering was new or worse, was simply asking the participant at 1 month and 1 year following head injury if they experienced headache, and if so if they also had experienced headache before the injury, and if the headache was worse than before.[18] This makes this study vulnerable for recall bias.[106] Furthermore, the assessment of headache was done with a single item in a symptom checklist containing 12 symptoms commonly reported following TBI.[18]

Another study from the USA compared post-concussion symptoms, including headache, 3 and 6 months post-injury, in patients exposed to MTBI and a control group with non-head injuries.[52] The authors found that in the MTBI group, headache occurred in 22.3% at 3 months and 22.9% at 6 months post-injury. The corresponding proportion in the control group were 11.5% at 3 months and 9.7% at 6 months.[52] The authors provided no statistics to show whether the difference between the groups was statistically significant. The assessment of headache was done from one item in the Rivermead Post-Concussion Symptoms Questionnaire.[52]

5.2.2 Relation to head injury severity

Some prior studies have shown an inverse dose-response relationship between the severity of head injuries and development of persistent headache.[14,114,123]

In Paper I, when doing a separate analysis with head injury in categories according to head injury severity we observed an even greater odds of headache for individuals with mild head injury than for all individuals exposed to head injury regardless of severity. Individuals with mild head injury were also more likely to have CDH, even after the participants with medication overuse were removed from the analysis. Individuals exposed to a moderate or severe head injury did not have increased odds of headache compared to controls. We experienced the same situation in Paper II. When doing a separate analysis with head injury in categories according to head injury severity we observed an even greater odds of stable headache and exacerbation of headache status for individuals with mild head injury than all individuals exposed to head injury regardless of severity. Individuals with mild head injury also were more likely to have

new onset of headache compared to controls. There was no significant relationship between moderate head injury and any of the headache trajectories. This seems to confirm the paradoxical finding in earlier studies of a lack of a positive dose-response relationship between head injury severity and HAIH.[14,114,123] However, the analyses in both Paper I and Paper II included few moderate and severe head injuries, which gives low power. Furthermore, the classification of head injury severity has differed widely, which makes comparisons between studies difficult. [14,114,123]

Various hypotheses regarding headache after head injury suggest that brain tissue damage leads, through different mechanisms, to the development of headache. If so, one would expect a dose-response relationship between head injury severity and development of HAIH. Hence, our finding of an inverse dose-response relationship challenges this hypothesis. What other differences between patients with moderate or severe head injury versus mild head injury could explain this inverse dose-response relationship? It is likely that persons experiencing a mild head injury return earlier to work or school than those with a more severe head injury. Going back to normal life too soon, could possibly result in stress that could trigger a headache. A theory also evolved around stress is that patients with mild head injuries more often remember their accident than those with more severe injuries. Could this in some patients be stressful enough to trigger a headache? Patients with a moderate or severe head injury, especially the most severe injuries are most often admitted to hospital the first weeks following their head injury. While admitted to the hospital they will most likely be treated for any pains they might have. Could liberal use of analgesics the first few weeks post-injury be protective of the development of persistent HAIH? This hypothesis is strengthened by Paper III, where we found that having acute HAIH is a significant positive predictor of persistent HAIH. Another way of interpreting the lower prevalence of headache suffering among patients with a previous moderate or severe (in relationship to mild) head injury is that they may tend to under-report headache as a 'suffering' because of other more dominating sequelae.

5.2.3 Classification of HAIH into primary headaches

When headaches were classified according to criteria for primary headache disorders in Paper I, the higher occurrence of headache among individuals exposed to head injury was only evident for migraine, with the exception of TTH in the most recent injuries.

Among those in the MTBI group with exacerbation of headache in Paper III, migraine was the most common phenotype, followed by TTH. This is in accordance with several studies published in recent years that report migraine as the most common persistent headache phenotype after head injury.[38,62,66,67,114] However, there are also some studies where TTH was reported as the most common phenotype.[3,42,60] In all three papers in this thesis, every participant with headache suffering was registered with only one headache diagnosis. In studies where several headache phenotypes were registered, it was found that between 27-75% of the patients had more than one headache phenotype after head injury.[9,14]

Classifying a secondary headache according to criteria for primary headache disorders may seem unimportant, but at the moment, our only treatment strategy for HAIH is to treat the patient as one would treat a patient with a primary headache disorder of similar phenotype.[68] A symptom-based classification may be helpful for establishing clinically relevant endpoints for research and clinical trials for effective therapies.[69] Furthermore, there are some studies suggesting that HAIH with migraine features has a more severe course with delayed recovery compared to other primary headache phenotypes.[77]

5.2.4 The role of medication overuse in HAIH

In Paper I, the results showed an association between both head injury and MOH and head injury and CDH. When all participants who fulfilled the criteria for MOH were removed from the CDH group, this association was no longer significant for any head injury and weakened for mild head injury. In Paper III, 8.6% of the subjects who reported exacerbation of headache the first 3 months post-injury, and 9.2% of those reporting exacerbation 3-12 months post-injury, reported MOH. This is considerably higher than 1.0%, which is reported among the general population in Nord-Trøndelag.[63]

In a population-based study from Norway that investigated the prevalence of secondary chronic headache; the authors showed that about half of the individuals with CDH caused by HAIH had a co-occurrence of MOH.[127] A retrospective study from the USA explored analgesic overuse as a potential cause of persistent headache after head injury among adolescents referred to a headache clinic following concussion.[37] The majority (70%) of their participants fulfilling the criteria for HAIH also had MOH.[37] However, in a

previously mentioned population-based study from the USA, where cases with CDH and a comparison group with episodic headache were asked about lifetime occurrence of head and neck injury, medication taken for headache or non-headache pain was equally likely in the CDH groups with and without lifetime occurrence of head and neck injury.[15]

This is a topic in need of further research, but the current findings could suggest that medication overuse can contribute to a development of CDH following head injury. There is reason to suggest that clinicians should be equally attentive to any medication overuse among patients with HAIH as with other headache disorders.

5.2.5 Predictors of headache following head injury

The incidence of MTBI is high, and a close follow-up of all patients would require major efforts from the health care service[11]. To identify patients in need of intervention, it is important to recognize those at risk of developing HAIH. Previous studies have identified several predictors from factors related to the injured person, e.g. sex, age and socioeconomic status, and related to the injury e.g. head injury severity and acute symptoms following the head injury. [17,18,38,67,81]

5.2.5.1 Pre-injury and demographic factors

Several primary headaches and especially migraine, are more prevalent among women than men.[47,63] In Paper III, we found that female sex was a significant positive predictor for acute HAIH. This is in line with several other studies that have shown female sex to be a risk factor for HAIH[18,38,46,81,119]. One study did not observe the same difference between the sexes[67]. In Paper III we also examined age as a predictor of acute and persistent HAIH, but found no association between age at injury and the development of HAIH. This is consistent with several other studies that examined whether the development of HAIH was related to age at injury.[38,81,105] However, one study found that individuals over age 60 were significantly less likely to report headache at both 3, 6 and 12 months following head injury.[67]

5.2.5.2 Acute symptoms

In Paper I, participants exposed to head injury that experienced nausea at admission, had higher odds of having headache at the time of HUNT3 compared to those not experiencing nausea at admission. This is in line with a prospective study from the

Netherlands that found the presence of nausea in the emergency room after mild TBI to be strongly associated with the severity of most post-traumatic complaints, including headache, after six months.[17] In Paper I, also headache and dizziness at admission were associated with headache at the time of HUNT3. This is in contrast with the same study from the Netherlands that found no significant association between headache and dizziness in the emergency room and headache after six months.[17] The Dutch study was small and did not have uninjured controls but their findings are in line with a cohort study from Norway that explored potential predictors of headache 22 years after hospitalization for head injury. The authors found no association between headache the first day after head injury and headache 22 years after the head injury.[81] Although headache, nausea and dizziness at admission may be consequences of the head injury, they can also represent an already existing primary headache disorder. An alternative way to interpret our results is that for some individuals with episodic migraine or TTH, the stressful circumstances of the accident and physical injury rather than the direct injury to the head may have triggered an episode of headache on the day of admission. Likewise, those with pre-existing CDH of any kind may have had an increased likelihood of reporting headache both at the day of admission and at follow-up even if there is no causal relationship with the injury to the head.

In Paper III, acute HAIH was a significant positive predictor for persistent HAIH. This is in line with the previously mentioned Norwegian study that examined predictors of headache 22 years following head injury.[81] In that study, the authors found that headache three months after the head injury were one of the strongest positive predictors of long-term headache.[81]

In Paper I, there was no association between cranial fracture or traumatic intracranial pathology at admission and headache at the time of HUNT3. This is consistent with the findings in Paper III, where pathological imaging findings (a combined variable for intracranial pathology and cranial fractures) on CT or MRI was a significant positive predictor of acute HAIH but not persistent HAIH. Our findings are in line with a prospective study without controls examining predictors of HAIH following moderate to severe TBI from the USA, where the authors found that the odds of a more severe headache at twelve months post-injury were not greater for the participants with face, skull or spine fractures.[119] Furthermore, in the Norwegian cohort mentioned above, the

authors showed that cranial fracture, paradoxically, seemed to be protective of long-term headache.[81] Our findings, however, are in contrast with a recent study from Korea, where the authors found that HAIH occurred more frequently 12 months post-injury in patients with minimal traumatic intracranial haemorrhage after MTBI than in those without[40].

5.2.5.3 Head injury severity

The role of head injury severity for the development of HAIH is discussed in greater detail in *5.2.2. Relation to head injury severity.* In Paper III, the duration of PTA and the GCS score were not significant predictors of acute or persistent HAIH. However, the OR for persistent HAIH among those with PTA >1 hour was 0.49. (95% CI 0.22-1.13) which could suggest that those in our study with a more severe MTBI are less likely to experience HAIH.

5.2.5.4 Multiple head injuries

In Paper I we saw that subjects having more than one head injury showed an even greater odds of headache compared to controls than all individuals exposed to head injury without specification of iteration. In Paper III, prior MTBI was a significant positive predictor of persistent HAIH. These findings are in line with several other studies: The previously mentioned retrospective study by Couch et al. that examined the risk of CDH found that the odds of CDH increased with the number of lifetime head or neck injuries.[15] In a study aiming to predict which head injury patients were at risk for developing post-concussion symptoms (with a median duration of 19 weeks), multiple head injuries was one of the predictors.[121] In a review on sports-related HAIH, the authors concluded that those with multiple concussions experienced HAIH more frequently than those with single concussions.[94]

Multiple head injuries as a risk factor for HAIH could represent a dose-response relationship or "biological gradient" and substitute head injury severity in the discussion about the dose-response relationship in the development of headache following head injury.

5.3 Is HAIH a valid and useful diagnosis?

The overall aim of the thesis was to study whether headache after head injury is a unique disease entity separate from the most common headache disorders.

The papers presented in this thesis are in my opinion an important contribution to the controversy around the ICHD-3 diagnosis "Headache attributed to traumatic injury to the head". In three population-based studies we have described that there is a difference in headache suffering between individuals exposed to head injury compared to non-exposed. We have, however, no conclusive results regarding the diagnosis persistent HAIH. While Paper I and Paper II support that this is a true secondary headache, Paper III does not find evidence for greater headache suffering among those exposed to head injury compared to non-exposed beyond three months post-injury. This could be due to the differences in study design between Papers I and II and Paper III, and thus the different profile of potential biases in the different designs. Even though we do not have an unambiguous conclusion for persistent HAIH, our response to the thesis' overall aim is that headache after head injury is a unique disease entity.

We have found that repeated head injuries increase the odds of headache suffering. This could be of great importance to individuals with professions especially exposed to head injuries, such as athletes or soldiers. Ours and others' findings of increased odds of headache after repeated injury suggest that individuals that have experienced one head injury, should avoid situations where they are at risk for another injury.

A description of a disease and a measure of prevalence is crucial to be able to start investigating the best ways to manage this particular disease. The finding that HAIH is a valid diagnosis is, in my opinion, a useful and important contribution in the following research efforts to better attend to this patient group.

6 Future perspectives

Future studies should focus on three main areas. Firstly, it is important to try to acquire knowledge of *underlying pathophysiological mechanisms* for HAIH. More specifically, does head injury evoke new pain generators in some of the individuals exposed to head injury, or is head injury rather a trigger of primary headache mechanisms, such as migraine, that without the head injury trigger would not have been expressed until several years later, or perhaps not at all? This is important knowledge to support what must be the second important future research perspective, namely *treatment*. It is my impression, that many physicians working with headache, experience that patients with HAIH are more difficult to treat than patients with primary headaches. To date, there are no large, randomized, controlled clinical trials on treatment of HAIH. The current treatment strategy is to treat HAIH as the primary headache it most resembles. But as we do not know what pathophysiological mechanisms cause the headache, nor do we have any good studies to aid the choice of treatment, the rationale underlying this treatment strategy is merely lack of knowledge that could be gained through randomized controlled trials.

Finally, acquiring knowledge of *predictors for development of HAIH* would make it possible to predict who among the many individuals exposed to head injuries each year, will develop HAIH. This can help identify individuals who will benefit from a closer follow-up. Identifying persons at risk of developing HAIH can thus aid the development of clinical guidelines for follow-up after mild head injury.

7 Responses to given aims

Our response to the thesis' overall aim is that headache after head injury is a unique disease entity.

7.1 Paper I:

Individuals exposed to head injury had higher odds of persistent headache. This was evident only for mild, not moderate or severe head injuries. When classifying headaches according to criteria for primary headache disorders, the higher occurrence of headache among individuals exposed to head injury was only evident for migraine, with the exception of TTH in the most recent injuries. Nausea or dizziness at admission and headache during the hospital stay were positive predictors of headache suffering in HUNT3 in the head injury group.

7.2 Paper II:

Individuals exposed to head injury were more likely to have exacerbation of headache status and stable headache suffering compared to controls. In separate analyses with head injury in categories according to head injury severity, individuals with mild head injury had an even greater odds of stable headache and exacerbation of headache than all individuals exposed to head injury regardless of severity. Individuals with mild head injury also were more likely to have new onset of headache compared to controls.

7.3 Paper III:

There was a significantly larger increase in odds of headache during the first 3 months post-injury versus pre-injury status for the MTBI group, compared to trauma and community controls. However, the odds ratio of headache from pre-injury status to the period 3-12 months after trauma did not differ between the groups. Female sex and

pathological imaging findings on CT or MRI were positive predictors for acute HAIH. Prior MTBI, being injured under the influence of alcohol, and acute HAIH were positive predictors for persistent HAIH. Hence, exacerbation of headache during the first few months after MTBI is likely related to the trauma, but even though acute HAIH is a risk factor for persistent HAIH, chances are good for improvement of their headache before reaching 12 months post-injury.

8 Appendix

Supplementary Table 1 Variables collected from medical records

	Variable	Categories
Information regarding the trauma	Date of trauma	
	Age at trauma	
	Hospital	Levanger/Namsos/St. Olavs Hospital
	Length of hospital stay	<24/24-48/>48 hours
	External force	Head being struck by an object/Head striking an object/Brain undergoing an acceleration or deceleration movement without direct external trauma to the head/Foreign body penetrating the head/Blast or explosion/Other force yet to be defined
	Mechanism of injury	Falling/Traffic accident (including bicycle accidents)/Assault/Other
	If fall, height of head over impact target	No fall (or most likely not)/< 2 m (including fall down stairs)/ ≥ 2 m
	Accident at place of employment	No (or most likely not)/Yes
	Psychotropic drugs, incl. alcohol[1]	No (or most likely not)/Yes
Symptoms and signs of influence on brain function	Alteration in mental state[2]	No (or most likely not)/Yes
	Glasgow Coma Scale (GCS) score[3]	15 (or most likely) / 14 / 13 / 9-12 / 3-8
	Sedated (and intubated) prior to admission[4]	No (or most likely not)/Yes
	Retrograde amnesia	No (or most likely not)/Yes
	Post-traumatic amnesia (PTA)	No (or most likely not)/<24/24-48/ > 48 hours/PTA occurred but with unknown duration
	Loss of consciousness (LOC)	None (or most likely not)/ < 5 min/ ≥5 min – 30 min/ ≥30min
	Vomiting and/or nausea	No (or most likely not)/Yes
	Dizziness[5]	No (or most likely not)/Yes
	Neurologic deficits acute	No (or most likely not)/Yes (and not clearly reconsidered later)
Radiology[6]	Cerebral CT	Not done (or most likely not)/Normal (i.e. no signs of trauma)/Pathological (traumatic findings)
	Cerebral MRI	
	CT or X-ray of facial bones	
	Plain X-ray of head	
	Epidural hematoma	No/Yes, not operated/Yes, operated/CT or MRI not done
	Subdural hematoma	

	Subarachnoid haemorrhage	
	Brain contusion	
	Intracerebral hematoma	
	Cranial fracture	No/Yes, fracture of neurocranium (radiological and/or clinical findings)/Yes, fracture of viscerocranium (radiological and/or clinical findings)/Plain X-ray, CT or MRI not done
Surgery	Surgery of the head	No/Only suturing (and cleaning) of superficial wounds/More than treatment of superficial wounds but not neurosurgery/Neurosurgery
Signs of permanent influence of brain function[7]	Neurological sequelae	No (or most likely not)/Yes
	Cognitive sequelae	
Diagnosis	Primary diagnosis	
	Other relevant diagnosis	
	Number of ICD-9 or ICD-10 codes	
Classification of head trauma	Subtype of head injury according to HISS	No head injury (or most likely not)/Minimal/Mild/Minimal or mild/Moderate/Severe or critical
	Subtype of head injury categorized according to ICHD-3 beta	No head injury (or most likely not)/Mild/Moderate or severe

[1] Anamnestic data, clinical signs or as confirmed by laboratory testing. [2] At the scene or at admission. [3]At admission. [4]Patients that were sedated without being intubated is also recorded as yes. [5]Patients subjective feeling of dizziness. [6]Based on information in the medical records. [7]At discharge from acute treatment.

HODEPINE

Har du vært plaget av hodepine i løpet av de siste 12 måneder? 209

Ja, anfallsvis (migrene)..... ☐ 1

Ja, annen slags hodepine.... ☐ 2

Nei ..... ☐ 3

Antall anfall siste 12 mndr. 210 ☐

Hvis «Nei»: Gå til MUSKEL-/SKJELETTPLAGER

Omtrent hvor mange dager i pr. måned har du hodepine?

Mindre enn 7 dager ☐ 1 7 til 14 dager ☐ 2 Mer enn 14 d. ☐ 3

Hvor lenge varer hodepinen vanligvis hver gang? 213

Mindre enn 4 timer ☐ 1 4 timer–3 døgn ☐ 2 Mer enn 3 døgn ☐ 3

Hvor ofte er hodepinen preget av eller ledsaget av:

Ett kryss på hver linje	*Sjelden eller aldri*	*Av og til*	*Ofte*
bankende/dunkende smerte 214	☐	☐	☐
pressende smerte	☐	☐	☐
halvsidighet, alltid samme side	☐	☐	☐
halvsidighet, vekselvis h. og v. side	☐	☐	☐
smerter i «hele hodet»	☐	☐	☐
kvalme 219	☐	☐	☐
lys- og/eller lydskyhet	☐	☐	☐
forverring ved fysisk aktivitet.....	☐	☐	☐
synsforstyrrelser *før* hodepine 222	☐	☐	☐

Hvor mange tabletter/stikkpiller har du eventuelt brukt av disse medisinene *alt i alt i løpet av den siste måneden*?

Skriv 0 hvis du ikke har brukt medisinen.

Cafergot 223 ☐ Anervan 225 ☐ Imigran 227 ☐

Supplementary Figure 1 Headache questionnaire in HUNT2

HODEPINE

17 Har du vært plaget av hodepine det siste året? — Ja ☐ Nei ☐
Hvis nei, gå til spørsmål 24.

Hvis ja:
Hva slags hodepine:
Migrene ☐
Annen hodepine ☐

18 Omtrent antall dager pr. måned med hodepine:
Mindre enn 1 dag ☐ 7-14 dager ☐
1-6 dager ☐ Mer enn 14 dager ☐

19 Hvor sterk er hodepina vanligvis?
Mild *(hemmer ikke aktivitet)* ☐
Moderat *(hemmer aktivitet)* ☐
Sterk *(forhindrer aktivitet)* ☐

20 Hvor lenge varer hodepina vanligvis?
Mindre enn 4 timer ☐ 1-3 døgn ☐
4 timer – 1 døgn ☐ Mer enn 3 døgn ☐

21 Er hodepina vanligvis preget av eller ledsaget av:
(Sett ett kryss pr. linje)

	Ja	Nei
Bankende/dunkende smerte?	☐	☐
Pressende smerte?	☐	☐
Ensidig smerte (høyre eller venstre)?	☐	☐
Forverring ved moderat fysisk aktivitet?	☐	☐
Kvalme og/eller oppkast?	☐	☐
Lys- og lydskyhet?	☐	☐

22 Før eller under hodepina; kan du ha forbigående:
(Sett ett kryss pr. linje)

	Ja	Nei
Synsforstyrrelse? *(takkede linjer, flimring, tåkesyn, lysglimt)*	☐	☐
Nummenhet i halve ansiktet eller i handa?	☐	☐

23 Angi hvor mange dager du har vært borte fra arbeid eller skole siste måned på grunn av hodepine: ☐ dager

Supplementary Figure 2 Headache questionnaire in HUNT3

1. Har du vært plaget av hodepine det siste året før hodeskaden din? ☐ Ja ☐ Nei

   Hvis ja:

2. Hva slags hodepine? (Sett to kryss hvis du har opplevd begge alternativer)
   ☐ Migrene ☐ Annen hodepine

3. Omtrent antall dager pr. måned med hodepine
   ☐ Mindre enn 1 dag ☐ 1-6 dager ☐ 7-14 dager ☐ Mer enn 14 dager

4. Hvor sterk er hodepinen vanligvis?
   ☐ Mild (hemmer ikke aktivitet) ☐ Moderat (hemmer aktivitet) ☐ Sterk (forhindrer aktivitet)

5. Hvor lenge varer hodepinen vanligvis?
   ☐ Mindre enn 4 timer ☐ 4 timer - 1 døgn ☐ 1-3 døgn ☐ Mer enn 3 døgn

6. Er hodepinen vanligvis preget eller ledsaget av:
   (Sett ett kryss pr. linje)

Bankende/dunkende smerte?	☐ Ja	☐ Nei
Pressende smerte?	☐ Ja	☐ Nei
Ensidig smerte(høyre eller venstre)?	☐ Ja	☐ Nei
Forverring ved moderat fysisk aktivitet?	☐ Ja	☐ Nei
Kvalme og/eller oppkast?	☐ Ja	☐ Nei
Lys- og lydskyhet?	☐ Ja	☐ Nei

7. Før eller under hodepinen kan du ha forbigående:
   (Sett ett kryss pr. linje)

Synsforstyrrelse? *(takkede linjer, flimring, tåkesyn, lysglimt)*	☐ Ja	☐ Nei
Nummenhet i halve ansiktet eller hånden?	☐ Ja	☐ Nei

8. Angi hvor mange dager du har vært borte fra arbeid eller skole siste måned på grunn av hodepine: ☐☐ dager

9. Angi hvor mange dager du har tatt smertestillende medikamenter eller migrenemedisin siste måned på grunn av hodepine: ☐☐ dager

Supplementary Figure 3 Headache questionnaire at baseline in Trondheim MTBI follow-up study

1. **Har du vært plaget av hodepine på noe tidspunkt etter skaden (siste 3 måneder)?** Her tenker vi på alle hodepineplager siste 3 måneder, ikke bare plager du relaterer til skaden. (Hvis nei, gå til spørsmål 10) ☐ Ja ☐ Nei

Hvis du ikke lenger er plaget av hodepine nå, men har vært det på noe tidspunkt etter skaden, beskriv hodepinen slik den var da du opplevde den.

2. Hva slags hodepine? (Sett to kryss hvis du har opplevd begge alternativer)
   ☐ Migrene ☐ Annen hodepine

3. Omtrent antall dager pr. måned med hodepine
   ☐ Mindre enn 1 dag ☐ 1-6 dager ☐ 7-14 dager ☐ Mer enn 14 dager

4. Hvor sterk har hodepinen du har opplevd de 3 siste måneder vanligvis vært?
   ☐ Mild (hemmer ikke aktivitet) ☐ Moderat (hemmer aktivitet) ☐ Sterk (forhindrer aktivitet)

5. Hvor lenge har hodepinen du har opplevd de 3 siste måneder vanligvis vart?
   ☐ Mindre enn 4 timer ☐ 4 timer - 1 døgn ☐ 1-3 døgn ☐ Mer enn 3 døgn

6. Har hodepinen du har opplevd de 3 siste måneder vanligvis vært preget eller ledsaget av: (Sett ett kryss pr. linje)

Bankende/dunkende smerte?	☐ Ja	☐ Nei
Pressende smerte?	☐ Ja	☐ Nei
Ensidig smerte(høyre eller venstre)?	☐ Ja	☐ Nei
Forverring ved moderat fysisk aktivitet?	☐ Ja	☐ Nei
Kvalme og/eller oppkast?	☐ Ja	☐ Nei
Lys- og lydskyhet?	☐ Ja	☐ Nei

7. Før eller under hodepinen du har opplevd siste 3 måneder; kan du ha forbigående: (Sett ett kryss pr. linje)

Synsforstyrrelse? *(takkede linjer, flimring, tåkesyn, lysglimt)*	☐ Ja	☐ Nei
Nummenhet i halve ansiktet eller hånden?	☐ Ja	☐ Nei

8. Angi hvor mange dager du har vært borte fra arbeid eller skole siste måned på grunn av hodepine: ☐☐ dager

9. Angi hvor mange dager du har tatt smertestillende medikamenter eller migrenemedisin siste måned på grunn av hodepine: ☐☐ dager

10. Fikk du ny eller forverret hodepine etter skaden? ☐ Ja ☐ Nei
    (hvis ja, svar på spørsmål 11 og 12)

11. Dersom hodepinen har opphørt, eller blitt som før skaden, hvor lang tid etter skaden tok det? ☐

12. Hvordan plages du av hodepine nå sammenlignet med før skaden?
    ☐ Likt som før skaden
    ☐ Verre enn før skaden
    ☐ Bedre enn før skaden

Supplementary Figure 4 Headache questionnaire at 3 months in Trondheim MTBI follow-up study

1. **Har du vært plaget av hodepine på noe tidspunkt siden forrige samtale (siste 9 måneder)?** ☐ Ja ☐ Nei
   (Hvis nei, gå til spørsmål 10)

Hvis du ikke lenger er plaget av hodepine nå, men har vært det på noe tidspunkt etter skaden, beskriv hodepinen slik den var da du opplevde den.

2. Hva slags hodepine? (Sett to kryss hvis du har opplevd begge alternativer)
   ☐ Migrene ☐ Annen hodepine

3. Omtrent antall dager pr. måned med hodepine
   ☐ Mindre enn 1 dag ☐ 1-6 dager ☐ 7-14 dager ☐ Mer enn 14 dager

4. Hvor sterk har hodepinen du har opplevd siste 9 måneder vanligvis vært?
   ☐ Mild (hemmer ikke aktivitet) ☐ Moderat (hemmer aktivitet) ☐ Sterk (forhindrer aktivitet)

5. Hvor lenge har hodepinen du har opplevd siste 9 måneder vanligvis vart?
   ☐ Mindre enn 4 timer ☐ 4 timer - 1 døgn ☐ 1-3 døgn ☐ Mer enn 3 døgn

6. Har hodepinen du har opplevd det siste 9 mnd vanligvis vært preget eller ledsaget av:
   (Sett ett kryss pr. linje)

Bankende/dunkende smerte?	☐ Ja	☐ Nei
Pressende smerte?	☐ Ja	☐ Nei
Ensidig smerte(høyre eller venstre)?	☐ Ja	☐ Nei
Forverring ved moderat fysisk aktivitet?	☐ Ja	☐ Nei
Kvalme og/eller oppkast?	☐ Ja	☐ Nei
Lys- og lydskyhet?	☐ Ja	☐ Nei

7. Før eller under hodepinen du har opplevd siste 9 måneder; kan du ha forbigående:
   (Sett ett kryss pr. linje)

Synsforstyrrelse? *(takkede linjer, flimring, tåkesyn, lysglimt)*	☐ Ja	☐ Nei
Nummenhet i halve ansiktet eller hånden?	☐ Ja	☐ Nei

8. Angi hvor mange dager du har vært borte fra arbeid eller skole siste måned på grunn av hodepine: ☐☐ dager

9. Angi hvor mange dager du har tatt smertestillende medikamenter eller migrenemedisin siste måned på grunn av hodepine: ☐☐ dager

10. Fikk du ny eller forverret hodepine etter skaden? ☐ Ja ☐ Nei
    (hvis ja, svar på spørsmål 11 og 12)

11. Dersom hodepinen har opphørt, eller blitt som før skaden, hvor lang tid etter skaden tok det? ☐

12. Hvordan plages du av hodepine nå sammenlignet med før skaden?
    ☐ Likt som før skaden
    ☐ Verre enn før skaden
    ☐ Bedre enn før skaden

Supplementary Figure 5 Headache questionnaire at 12 months in Trondheim MTBI follow-up study

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Headaches in patients with previous head injuries: A population-based historical cohort study (HUNT)

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Abstract

Background: Headache attributed to head injury is claimed to be among the most common secondary headache disorders, yet available epidemiological evidence is scarce. We evaluated the prevalence of headache among individuals previously exposed to head injury by a comparison to an uninjured control group.

Methods: This population-based historical cohort study used data from hospital records on previous exposure to head injury linked to a large epidemiological survey with data on headache occurrence. Participants without head injury, according to hospital records, were used as controls. The head injuries were classified according to the Head Injury Severity Scale (HISS) and the International Classification of Headache Disorders (ICHD-3 beta). Binary logistic regression was performed to investigate the association between headache and head injury, controlling for potential confounders.

Results: The exposed group consisted of 940 individuals and the control group of 38,751 individuals. In the multivariate analyses, adjusting for age, sex, anxiety, depression and socioeconomic status, there were significant associations between mild head injury and any headache, migraine, chronic daily headache and medication overuse headache.

Conclusion: Headache was more likely among individuals previously referred to a hospital for a mild head injury compared to uninjured controls.

Keywords

Epidemiology, headache, post-traumatic headache, head injuries, traumatic brain injury

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Introduction

Headache is very common in the general population and constitutes a large social and economic burden for the global society as well as the individual (1,2). Headache can either be primary, for example migraine or tension-type headache (TTH), or it can be secondary to another disorder. Headache attributed to head injury (the latter referred to as traumatic brain injury (TBI) if the brain is affected), is among the most common secondary headache disorders (3).

Traumatic brain injury (TBI) is a common and important global health issue and a major cause of morbidity (4,5). Headache is the most common symptom following TBI (6–8) and is often persistent (6,9). It is reported that 18–22% of the headaches attributed to traumatic injury to the head (HAIH) last for more than one year (10,11).

HAIH is defined in the current version of the International Classification of Headache Disorders (ICHD-3 beta) as a headache disorder with no defining clinical characteristics that starts within seven days of trauma or injury or after regaining consciousness (3).

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HAIH is defined as persistent if it continues beyond three months.

Only a small number of studies using non-injured comparison groups have investigated the causal relationship between head injury and headache (12,13), and few of them have shown a dose-response relationship (14). It has also been shown that HAIH does not differ from migraine and tension-type headache (TTH) based on clinical characteristics (10). Consequently, some experts are disputing the existence of HAIH, arguing that it may be nothing other than a primary headache being misattributed to a head injury (15).

Available epidemiological evidence on HAIH is mainly based on studies with methodological limitations such as small samples with a high risk of selection bias, and varying case definitions for both head injury and HAIH.

In this article we present the findings of the so far largest controlled, population-based study on HAIH. We specifically investigated whether the prevalence of headache and its subtypes was higher among persons previously exposed to head injury and whether this was influenced by injury characteristics.

Materials and Methods

Study design

This is a historical cohort study. Data from hospital records on exposure to head injury during the period 1988–2008 were assembled and linked to a large epidemiological survey, performed between 2006 and 2008, with validated data on the occurrence of headache. Participants without head injury, according to hospital records, were used as a control group.

The HUNT3 survey

The third Nord-Trøndelag Health Study (HUNT3) was a cross-sectional study performed between October 2006 and June 2008. All inhabitants of Nord-Trøndelag County above the age of 19 were invited to participate. There were more than 200 health-related questions, and among them there were 14 headache questions designed to establish whether the participants suffered from headache or not, and to classify the headache according to the International Classification of Headache Disorders (ICHD-II) (16). Details of this comprehensive health study, including non-respondents, are described elsewhere (17,18).

Head injury data collection

Inhabitants in Nord-Trøndelag who had answered the 14 headache questions in HUNT3 and also been exposed to a head injury during the period 1988–2008 were identified in 2012 by a computer-based search. This was performed as follows: The national 11-digit identification numbers of all patients who had received one or more diagnoses related to head injury at the outpatient or inpatient wards at the hospitals in Nord-Trøndelag (i.e. Levanger and Namsos) or the nearest university hospital (St. Olavs Hospital in Trondheim, Sør-Trøndelag) during the time period 1988–2008 were registered. From the list of identification numbers, a data manager at the HUNT Research Centre identified all individuals who had answered the headache questions in HUNT3. Initially, all participants with head injuries that had received diagnostic codes from the International Classification of Diseases 9 (ICD-9) and 10 (ICD-10) referring to trauma to the body above the neck were included. Participants with diagnostic codes without assumed influence of brain function were later removed and the final selection was done by search for ICD-9 codes 800–804, 850–854, 920 and 925, and ICD-10 codes S02, S06, S07, T02.0–T04.0, and T06.0. Exclusion criteria were chronic subdural hematoma, no contact with the hospital in the first 48 hours after injury, and no matching information about trauma in the text of the chart or lack of signs or symptoms of head injury noted in the medical record.

Data regarding the head injuries were collected from medical records. This was performed by two medical students (LHN and TP) and an experienced research nurse (GBG) in close dialogue with a neurologist with expertise in epidemiology and headache (ML) and a neurosurgeon with expertise in head injury (AV). All available information in the medical records was scrutinized. A total of 38 variables were recorded for each head injury (Supplementary Table 1). If the same individual had more than one head injury, up to three of the most recent head injuries were recorded in chronological order. We recorded any CT, MRI or X-ray-imaging associated with the head injury within three months after the injury. Clear clinical signs of cranial fractures (hemotympanum, clear bleeding from the auditory canal and leakage of cerebrospinal fluid) were regarded as cranial fractures even without imaging evidence. The head injuries were classified according to the Head Injury Severity Scale (HISS, 19), and to the ICHD-3 beta, which contains a relatively detailed classification of the head injury associated with the headache (3). Because medical records often contain insufficient information to correctly classify injury severity (20), we used the term ''most likely'' in some categories in order to be able to describe the acute symptoms and signs and classify the injury.

Headache diagnosis in HUNT3

Individuals who answered "yes" to the first screening question "Have you suffered from headaches during the last year?" answered the subsequent thirteen headache questions in HUNT3 that enabled the report of definite migraine, probable migraine and tension-type headache (TTH), according to the ICHD-II criteria (16). The participants were also asked to state the consumption of analgesics and over-the-counter (OTC) drugs during the last month. This enabled the report of medication overuse headache (MOH). Participants fulfilling both TTH and probable migraine criteria were classified as TTH. Participants were not specifically asked about the duration of untreated headache attacks, due to the fact that some individuals always use attack medication for their headaches. Because of this, the ICHD-II criteria for migraine were modified so that duration of less than four hours was also accepted. Chronic daily headache (CDH) was defined as headache occurring >14 days per month. The ICHD-II criteria for MOH were slightly modified so that they were based on OTC-medications only. This was due to lack of information about prescribed analgesics and triptans. Medication overuse was defined as OTC-medication use for headache or pains in muscles and joints ≥4 days per week during the last month. MOH was defined as CDH with medication overuse. The validity of these questionnaire-based diagnoses has been reported previously (21). For any headache, the sensitivity was 88% and specificity 86% (kappa value 0.70, 95% confidence interval (CI) 0.61–0.79); for migraine, the sensitivity was 51% and specificity 95% (kappa values 0.50, 95% CI 0.32–0.68); for TTH ≥ 1 day/month the sensitivity was 96% and specificity was 69% (kappa value 0.44, 95% CI 0.30–0.58), and for MOH the sensitivity was 75% and specificity was 99% (kappa value 0.75, 95% CI 0.30–1.00).

Statistical analysis

Descriptive statistics (mean with standard deviation) and chi-square test were used to characterize the sample. In the multivariate analyses, using binary logistic regression, we estimated the odds ratios (OR) with 95% CI for the association between head injury and its subcategories and each category of headache. Head injuries were also stratified on the basis of when it happened (the 50% most recent, i.e. ≤10 years before interview, and the 50% earliest head injuries, i.e. >10 years before interview). Persons not suffering from headache were used as reference category. We initially adjusted for age (continuous variable) and sex, and subsequently for other potential confounding factors identified previously (e.g. smoking (yes/no), body mass index (BMI, continuous variable), and total Hospital Anxiety and Depression Scale (HADS) score (categorized from continuous variable into three categories with score boundaries ≤16, 17–21 and ≥22). Further, to adjust for socioeconomic status, we included information on occupation (ten categories) and reclassified the subjects into an approximation of the international social class schema by Erikson, Goldthorpe and Portocarero (EGP) (22,23). The participants were classified into three categories: high social class (EGP I-II), medium social class (EGP III-IV) and lower social class (EGP V-VII).

Covariates that did not substantially change the estimated ORs separately or together (i.e. less than 0.05) were excluded from the final model. This was the case for smoking and BMI. Subjects with incomplete data for the HADS score variable were nevertheless included, as a separate missing category, in all analyses to reduce the impact of response bias. In all analyses, two-tailed *p*-values were calculated and a *p*-value of 0.05 or less was defined as statistically significant. Statistical analyses were performed with IBM® SPSS® Statistics 21.

Ethical approval

The study was approved by the Regional Committee for Medical and Health Research Ethics and by the HUNT Research Centre.

Results

Participants

The flow of participants through the different stages of the study is presented in Figure 1. There were 25,760 registered hospital-referred head injuries at Levanger and Namsos hospitals and 119,402 at St. Olavs hospital in Trondheim during the 20-year period. Linkage of the patients' national identification numbers to the HUNT database revealed that 2,889 of the persons with hospital-referred head injuries had answered the headache questions in HUNT3. Of them, 1,183 had a head injury with a diagnostic code reflecting assumed influence of brain function. Among these, 66 experienced their head injury after the HUNT3 survey and were thus not eligible, and 177 were excluded with regard to the exclusion criteria. The final exposed group ($n = 940$) and the unexposed group ($n = 38{,}751$) are presented in Table 1.

Head injuries

Among the 940 persons with head injuries, 55 had more than one head injury adding up to a total of 1,001 head injuries. Their severities according to HISS and

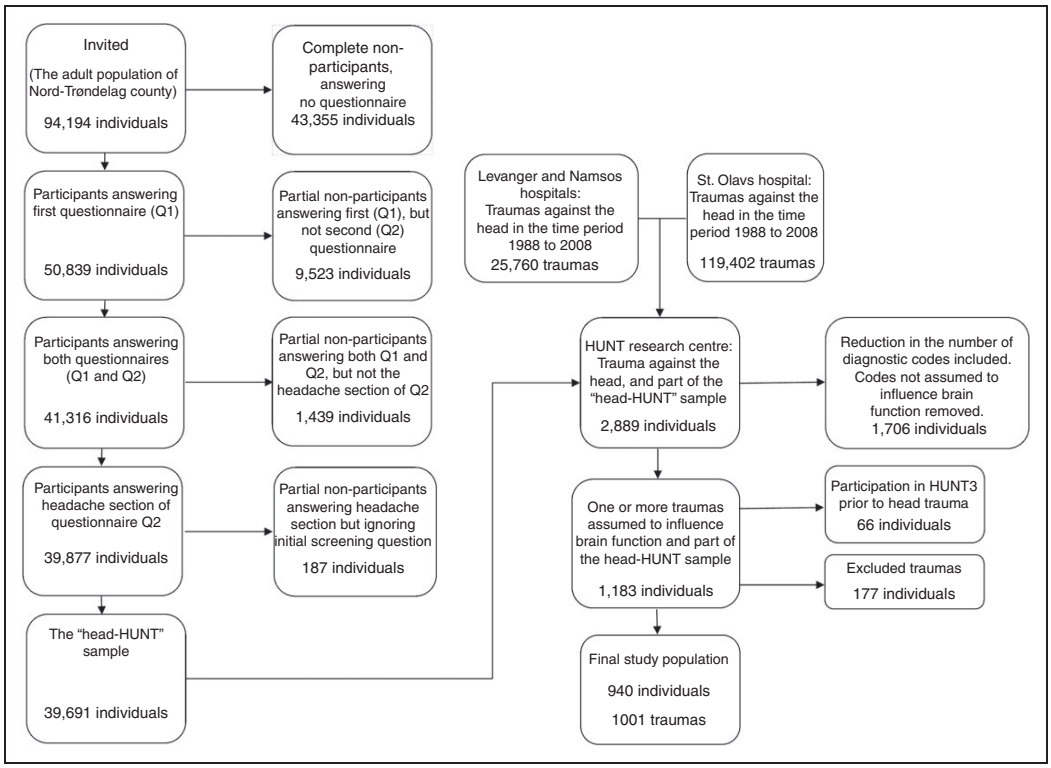

Figure 1. Flow of participants through the different steps of the HUNT3 headache survey and the different steps of identification of participants with head injuries.

ICHD-3 beta and acute symptoms following the head injury are reported in Table 2.

After the head injury, a CT scan was performed on 40% ($n = 380$), an MRI on 1% ($n = 6$) and a plain X-ray of the head on 11% ($n = 102$) of the patients. The scans revealed traumatic pathology in 11% ($n = 99$) of all patients in the cohort. In total, 6.5% ($n = 61$) had intracranial pathology: 30 patients had only intraparenchymal lesions (22 patients had brain contusions, four had intracerebral hematomas, four had both brain contusion and intracerebral hematoma), 14 had only extraparenchymal hemorrhages and 17 patients had both. 7.7% of all patients ($n = 72$) had cranial fractures (revealed either by imaging or clinical findings), and 3.3% ($n = 31$) had both cranial fracture and intracranial pathology.

In the year 2000, new guidelines for initial management of minimal, mild and moderate head injuries were implemented in Norway advocating more liberal use of CT imaging of the head (24). During the period 1988 through 2000, 30% had a CT examination ($n = 196$ out of 643), while from 2001 the proportion was 62% ($n = 184$ out of 297). During the first time period, 6% ($n = 37$) of all patients had imaging evidence of intracranial pathology compared to 8% from 2001($n = 23$), χ^2 (1) = 1.346, $p = 0.246$.

Headache diagnoses

In multivariate analyses adjusting for age, sex, HADS score and social class, the ORs of headache and migraine in HUNT3 were increased among individuals with head injury as compared to those without, evident only for those with mild head injury (Table 3). The OR of episodic migraine with frequency 1–14 days/month was nearly two-fold ($n = 90$ (14%), OR 1.77, 95% CI 1.37–2.28, $p < 0.001$) for those with mild head injury according to HISS compared to those without head injury. Subjects having more than one head injury showed an even stronger association with headache than any head injury without specification of iteration (Tables 3 and 4a). The head injuries ≤10 years before

Table 1. Demographics.

	Cases	Controls
Variable	N (%)	N (%)
Total number of subjects	940	38,751
Total number of head injuries	1,001	
Age at injury (first injury) (mean ± SD)	39.9 ± 19.6	
Age at participation in HUNT3 (mean ± SD)	50.6 ± 17.9	54.2 ± 15.6
Time from injury to HUNT3 (years) (mean ± SD)	10.3 ± 6.0	
Head injury >10 years before interview (years) (mean ± SD)	15.4 ± 2.8	
Head injury ≤10 years before interview (years) (mean ± SD)	5.1 ± 3.0	
Female	425 (45%)	21,808 (56%)
Social class by occupation[a]		
High	305 (32%)	13,215 (34%)
Medium	328 (35%)	14,872 (38%)
Low	249 (26%)	8,493 (22%)
Others[b]	58 (6%)	2,171 (6%)
HADS score (mean ± SD)	8.2 ± 5.8	7.3 ± 5.4
BMI (mean ± SD)	27.2 ± 4.6	27.2 ± 4.4
Smoking	280 (30%)	8,694 (22%)
Self-reported health poor or less than good	268 (29%)	9,806 (25%)

BMI: Body Mass Index; HADS: Hospital Anxiety and Depression Scale.
[a]The HUNT occupational classification reclassified into Erikson, Goldthorpe and Portocarero (EGP) social class schema (23,24).
[b]Full-time household workers, students, militaries, persons receiving social security and persons with missing data.

Table 2. Injury characteristics.

HISS classification[a]	
No head injury	3 (0.3%)
Minimal	110 (11.0%)
Mild	681 (68.0%)
Minimal or mild	44 (4.4%)
Moderate	109 (10.8%)
Severe	9 (0.9%)
Unknown	45 (4.5%)
ICHD 3-beta classification[a]	
No head injury	58 (5.8%)
Mild head injury	782 (78.1%)
Moderate or severe head injury	118 (11.8%)
Unknown	43 (4.3%)
Mechanism of injury[a]	
Fall	466 (46.6%)
Traffic accident	333 (33.3%)
Assault	66 (6.6%)
Other	126 (12.6%)
Unknown	10 (0.9%)
Acute symptoms[b]	
Headache during hospital stay	615 (65.4%)
Missing data	129 (13.7%)
Nausea	521 (55.4%)
Missing data	112 (11.9%)
Dizziness	265 (28.2%)
Missing data	307 (32.7%)
Alteration in mental state at the scene or at admission[c]	404 (43.0%)
Missing data	166 (17.7%)

HISS: Head Injury Severity Scale; ICHD 3-beta: International Classification of Headache Disorders, version 3-beta.
[a]Refers to number of head injuries and not number of patients.
[b]If several head injuries, only first head injury is counted.
[c]E.g. confusion, disorientation, slowed thinking, or somnolence.

interview were significantly associated with any headache as well as migraine and TTH, while the older head injuries (>10 years before interview) were only significantly associated with migraine (Tables 3 and 4b). The strongest association was found between mild head injury according to HISS and MOH (Table 4b). No significant relationship was found between head injury according to HISS and TTH for the overall period (Table 3).

Participants exposed to a mild head injury according to ICHD-3 beta had a significantly higher prevalence of migraine ($n = 126$ (17%), OR 1.58, 95% CI 1.27–1.97,

Table 3. Prevalence OR with 95% CI of headache disorders related to earlier head injury.

	Total no.[a]	Any headache			Migraine			Tension-type headache (TTH)			Other headaches		
		N	OR (95% CI)	*p*-value	N	OR (95% CI)	*p*-value	N	OR (95% CI)	*p*-value	N	OR (95% CI)	*p*-value
No head injury	38,751	13,833	Ref.		4,256	Ref.		6,114	Ref.		3,463	Ref.	
Any head injury	940	390	*1.19 (1.04–1.37)*	*0.013*	*151*	*1.47 (1.20–1.79)*	*<0.001*	162	1.11 (0.93–1.34)	0.25	77	0.99 (0.76–1.29)	0.92
Mild (HISS)	643	276	*1.28 (1.08–1.52)*	*0.004*	*112*	*1.66 (1.31–2.09)*	*<0.001*	106	1.10 (0.88–1.38)	0.41	48	1.10 (0.81–1.50)	0.56
Moderate/severe (HISS)	113	35	0.79 (0.52–1.20)	0.26	10	0.74 (0.37–1.49)	0.40	19	0.94 (0.56–1.58)	0.82	6	0.68 (0.29–1.57)	0.36
>1 head injury	55	33	*2.46 (1.38–4.40)*	*0.002*	*16*	*3.52 (1.70–7.29)*	*0.001*	11	1.96 (0.91–4.20)	0.084	6	2.13 (0.83–5.45)	0.11
Head injury >10 years before interview	470	190	1.07 (0.88–1.31)	0.48	79	*1.43 (1.09–1.88)*	*0.011*	69	0.89 (0.68–1.17)	0.42	42	1.03 (0.72–1.47)	0.88
Head injury ≤10 years before interview	470	200	*1.33(1.09–1.61)*	*0.005*	72	*1.51 (1.14–2.01)*	*0.005*	93	*1.36 (1.06–1.74)*	*0.015*	35	0.94 (0.64–1.38)	0.75

Adjusted for age, sex, social class by occupation and HADS score.
Other headaches: headaches that are not possible to classify as either migraine or TTH. HISS: Head injury severity scale.
[a]Number of patients, not of head injuries.

$p < 0.001$), CDH ($n = 32$ (4%), OR 1.89, 95% CI 1.30–2.76, $p = 0.001$) and MOH ($n = 16$ (2%), OR 1.98, 95% CI 1.17–3.32, $p = 0.010$). However, they did not have a significantly higher prevalence of TTH ($n = 127$ (18%) OR 1.12, 95% CI 0.91–1.38, $p = 0.30$) or CDH without MOH ($n = 14$ (2 %), OR 1.72, 95% CI 1.00–2.98, $p = 0.052$).

Participants previously exposed to a moderate or severe head injury according to both classifications did not have a significantly higher prevalence of headache. The figures for the HISS classification are given in Table 3, and for ICHD3 beta classification the OR was 1.05 ($n = 38$, 95% CI 0.54–2.04, $p = 0.89$).

Relationship between acute symptoms, imaging findings and current headache

Table 5 describes acute symptoms and imaging findings soon after the head injury. Previous head injuries were significantly associated with any headache only if they had been accompanied by headache during the hospital stay (OR 1.36, 95% CI 1.15–1.62), nausea at admission (OR 1.25, 95% CI 1.04–1.50) or dizziness at admission (OR 1.35, 95% CI 1.04–1.75). There was no significant association between any headache and acute alteration in mental state at the scene or at admission, cranial fractures or intracranial pathology (traumatic lesions).

Discussion

In this large population-based study, the main finding was that headache suffering was more likely among individuals exposed to a mild head injury than those not exposed.

Our results contrast with a previous Norwegian population-based study with an uninjured control group, which did not find an association between previous head injury and headache (12). However, that study had low statistical power since only 192 patients and controls were included and the control group differed significantly from the exposed group with regard to several important confounders.

We found that the association between headache and head injury was evident only for those sustaining mild head injury. This is in accordance with several earlier studies (10,25), although the comparability is limited by different methods for classification of head injury severity. We used both HISS and ICDH-3 beta as classification systems, as HISS is widely used among neurosurgeons whereas ICHD-3 is used by headache specialists (5,24). Using ICHD-3 beta for classification of head injury severity in our analysis resulted in the same conclusions as for HISS, with the one exception that a significant association between previous mild

Table 4a. Prevalence OR with 95% CI of different frequencies of headache (disregarding diagnosis) related to earlier head injury.

		Headache <1 day/month			Headache 1–6 days/month			Headache 7–14 days/month		
	Total no.[a]	N	OR (95% CI)	*p*-value	N	OR (95% CI)	*p*-value	N	OR (95% CI)	*p*-value
No head injury	38,751	3,053	Ref.		8,042	Ref.		1,679	Ref.	
Any head injury	940	71	1.00 (0.77–1.28)	0.97	*223*	*1.19 (1.01–1.41)*	*0.037*	51	1.28 (0.94–1.73)	0.12
Mild (HISS)	645	51	1.08 (0.80–1.47)	0.60	151	1.22 (1.00–1.49)	0.054	36	1.35 (0.94–1.94)	0.10
Moderate/severe (HISS)	109	11	1.12 (0.59–2.15)	0.72	20	0.83 (0.50–1.38)	0.47	3	–	
>1 head injury	55	4	–		*20*	*2.82 (1.47–5.41)*	*0.002*	6	–	
Head injury >10 years before interview	470	27	0.70 (0.47–1.05)	0.087	117	1.16 (0.93–1.46)	0.19	22	1.08 (0.69–1.69)	0.75
Head injury ≤10 years before interview	470	44	1.33 (0.96–1.84)	0.092	106	1.23 (0.97–1.56)	0.094	29	1.49 (0.99–2.23)	0.054

Adjusted for age, sex, social class by occupation and HADS score. HISS: Head injury severity scale.
[a]Number of patients, not of head injuries.

Table 4b. Prevalence OR with 95% CI of chronic daily headache (CDH) (disregarding diagnosis) and medication overuse[b] headache (MOH) related to earlier head injury.

		Chronic daily headache (CDH)[a] including medication overuse headache			Medication overuse[b] headache (MOH)			Chronic daily headache (CDH)[a] without medication overuse headache		
	Total no.[c]	N	OR (95% CI)	*p*-value	N	OR (95% CI)	*p*-value	N	OR (95% CI)	*p*-value
No head injury	38,751	933	Ref.		459	Ref.		439	Ref.	
Any head injury	940	*41*	*1.87 (1.37–2.61)*	*<0.001*	*22*	*2.10 (1.34–3.28)*	*0.001*	17	1.62 (0.98–2.67)	0.058
Mild (HISS)	645	*34*	*2.33 (1.61–3.37)*	*<0.001*	*18*	*2.55 (1.55–4.19)*	*<0.001*	*14*	*2.01 (1.16–3.49)*	*0.013*
Moderate/severe (HISS)	109	1	–		1	–		0	–	
>1 head injury	55	3	–		0	–		3	–	
Head injury >10 years before interview	470	*22*	*1.95 (1.24–3.07)*	*0.004*	*10*	*1.96 (1.02–3.75)*	*0.044*	*11*	*1.98 (1.07–3.69)*	*0.031*
Head injury ≤10 years before interview	470	*19*	*1.77 (1.09–2.87)*	*0.020*	*12*	*2.23 (1.22–4.08)*	*0.009*	6	–	

Adjusted for age, sex, social class by occupation and HADS score. HISS: Head injury severity scale.
[a]Headache on ≥15 days/month.
[b]Medication overuse is estimated based on medications used for headache or pain in muscles and joints.
[c]Number of patients, not of head injuries.

head injury and CDH without medication overuse was no longer observed.

When classifying the headaches according to criteria for primary headache disorders, the higher occurrence of headache among individuals exposed to head injury was only evident for migraine, with the exception of TTH in the most recent injuries. This is in accordance with several studies published in recent years that report migraine as the most common headache phenotype after head injury (6,9,26,27). This is in contrast with earlier studies where TTH was reported as the most common (8,28,29).

Headache, nausea or dizziness at admission was associated with headache at the time of HUNT3, while alteration in mental state, cranial fracture, or intracranial pathology (traumatic lesions) was not. A study from 2002 found that the presence of nausea in the emergency room after mild TBI was strongly associated with the severity of most post-traumatic complaints, including headache, after six months, while headache and dizziness in the emergency room were not significantly associated. However, the study was small and did not have uninjured controls (7). Although headache, nausea and dizziness at admission

Table 5. Prevalence OR with 95% CI of headache following head injury with or without proposed risk factors for headache.

		Any headache			
	Total no.[b]	N	OR	95% CI	*p*-value
Glasgow Coma Scale (GCS) score at admission					
No head injury	38,751	13,833	Ref.		
GCS score 15[a]	776	326	1.21	1.04–1.41	*0.015*
GCS score 14	106	44	1.29	0.86–1.94	0.22
GCS score ≤13	40	11	0.65	0.32–1.35	0.25
Missing	18				
Headache during hospital stay					
No head injury	38,751	13,833	Ref.		
Head injury without headache[a]	325	112	0.92	0.72–1.17	0.47
Head injury with headache	615	278	1.36	1.15–1.62	*<0.001*
Nausea at admission					
No head injury	38,751	13,833	Ref.		
Head injury without nausea[a]	419	162	1.13	0.92–1.39	0.26
Head injury with nausea	521	228	1.25	1.04–1.50	*0.020*
Dizziness at admission					
No head injury	38,751	13,833	Ref.		
Head injury without dizziness[a]	675	279	1.14	0.97–1.34	0.13
Head injury with dizziness	265	111	1.35	1.04–1.75	*0.024*
Alteration in mental state at the scene or at admission					
No head injury	38,751	13,833	Ref.		
Head injury without alteration in mental state[a]	536	220	1.21	1.00–1.45	*0.046*
Head injury with alteration in mental state	404	170	1.18	0.95–1.45	0.13
Cranial fracture					
No head injury	38,751	13,833	Ref.		
Head injury without cranial fracture[a]	868	364	1.18	1.02–1.37	*0.024*
Head injury with cranial fracture	72	26	1.33	0.81 – 2.20	0.27
Intracranial pathology[c]					
No head injury	38,751	13,833	Ref.		
Head injury without intracranial traumatic lesion[a]	880	370	1.20	1.04–1.38	*0.014*
Head injury with intracranial traumatic lesion	60	20	1.13	0.64–2.00	0.67

Adjusted for age, sex, social class by occupation and HADS score. [a]Or most likely. [b]Refers to number of patients and not number of head injuries. [c]Subdural hematoma, epidural hematoma, subarachnoid haemorrhage and cortical contusions or intracerebral hematoma. Missing data are interpreted as not having the symptom or finding.

may be consequences of the head injury, they can also represent an already existing primary headache disorder. Among some individuals with episodic migraine or TTH, the stressful circumstances of the accident and physical injury rather than the direct injury to the head may have triggered an episode of headache on the day of admission. Likewise, those with pre-existing CDH of any kind may have had an increased likelihood of reporting headache both at the day of admission and at follow-up even if there is no causal relationship with the injury to the head. In a study from 2005, Nestvold et al. (30) studied predictors of headache 22 years after hospitalization for head injury. They found no association between headache the first day after head injury and headache 22 years after the head injury. Cranial fracture seemed to be protective of long-term headache. We did not find cranial fracture to be either protective or a risk factor for headache.

Our study, and others like it, may be subject to a selection bias because individuals with headache and nausea after a head trauma may be more likely to seek medical advice and also to be referred to hospital. Since pre-traumatic headache seems to be a

strong risk factor for headache after head injury (31), this may have contributed to our finding of a somewhat higher prevalence of headache after head injury.

Having had multiple head injuries increased the association to headache. This may represent a "biological gradient" in support of a causal relationship according to the Bradford Hill criteria (32). A recent study showed that soldiers with two or more mild TBIs experienced significantly more post-traumatic symptoms than those with a single mild TBI only (33). However, this may also be due to a reinforcement of the selection bias mentioned above. Another similar study could not confirm this phenomenon statistically (34).

The major strengths of this study were the population-based design, the large sample size, and the use of validated headache diagnoses. Selective participation in HUNT3 due to headache status seems unlikely, because the headache questions were a minor part of a survey with more than 200 health related questions. It was also an advantage that head injury was not mentioned in HUNT3, as this might have introduced a recall bias (e.g. those remembering their head trauma being more likely to recall suffering from headache). We had extensive objective and previously documented information on each head injury, retrieved from medical records, thereby eliminating recall bias. This also enabled us to classify most of the cases both according to HISS and ICHD-3 beta. We had information on medication overuse and were able to distinguish medication overuse headache from other chronic daily headache.

The study also has some limitations. We were not able to determine time of onset of the headaches. This has two consequences, the first one being that the headache could have been present already before the head injury. Secondly, we cannot determine if the onset of headache was within seven days after head injury, which is the criterion for classifying a headache as attributed to traumatic injury to the head, according to ICHD-3 beta (3). However, several studies have indicated that this criterion may be too strict (9,35). Moreover, patients with chronic headaches had to be pooled into one CDH category, because only seven persons with chronic migraine and 16 with chronic TTH had had any trauma. This sample size was too small for drawing statistical conclusions about possible associations to previous trauma. Since it is difficult in epidemiological studies to establish precise diagnosis among persons with very frequent headache, headaches occurring >14 days/month are often pooled into one category. However, the low number of events in some subgroups, (e.g. moderate/severe head traumas and subjects with headache >14 days/month), made it difficult to draw firm conclusions with regard to their associations, despite pooling headaches into one CDH category in this study. A further limitation was that medications other than OTC-analgesics could not be considered in the definition of MOH because there was no information available about triptans or other prescription drugs in the present HUNT dataset. Furthermore, when retrieving information about the head injury from medical records, there is a risk of not capturing relevant information. Missing data may have led to overrepresentation of certain symptoms because the physicians were more likely to make a note in the medical record of a present symptom than an absent one. However, the proportion of data missing was low (Table 2). Generalization of results should be performed with caution, since only 42% of the adults invited to HUNT3 answered the headache questionnaire. Furthermore, patients without referral to hospital were not captured, and those had presumably mostly minimal or mild head injuries and not moderate or severe head injuries. The results might have been different if we had been able to include all persons in the population with minimal or mild traumas, provided that there is, as we have argued above, a selective inclusion of persons in whom such events elicit headache. However, it is unrealistic to capture in a population-based survey all persons who do not seek medical help after a trauma. Finally, during the data collection, it was not registered which of the four exclusion criteria that was applied when persons were excluded.

In conclusion, the present study indicates that mild but not moderate or severe injuries are associated with persistent headache. It can, however, not be excluded that cases with mild head injuries already suffering from primary headache came to the hospital more often. A large cohort-study is needed to follow a population which is known to be headache free and explore whether subjects who are exposed to a head injury more often develop persistent headache than the surrounding population.

Headache has high personal and societal costs because it leads to absence from work and social activities and patients with mild TBI present daily at emergency departments (1,2). Headache attributed to mild traumatic injury to the head may thus be a significant public health issue, and it has also important medico-legal implications. Further epidemiological research aiming to elucidate whether there is a causal association is urgently needed.

Key findings

- Headache suffering was more likely among individuals exposed to a mild head injury than those not exposed.
- The association between headache and head injury was not evident for those sustaining moderate or severe head injury.
- Migraine was the most common headache phenotype after head injury.
- Headache, nausea or dizziness at admission was associated with headache after head injury, while alteration in mental state, cranial fracture, or intracranial pathology (traumatic lesions) was not.

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Declaration of conflicting interests

No sources of funding were used to conduct this study. All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that (1) they have no support from any private company for the submitted work; (2) they have no conflicts of interest that are directly relevant to the content of this study; and (3) their spouses, partners, or children have no financial relationships that may be relevant to the submitted work.

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Paper II

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RESEARCH ARTICLE Open Access

Headache following head injury: a population-based longitudinal cohort study (HUNT)

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Abstract

Background: Headache is the most frequent symptom following head injury, but long-term follow-up of headache after head injury entails methodological challenges. In a population-based cohort study, we explored whether subjects hospitalized due to a head injury more often developed a new headache or experienced exacerbation of previously reported headache compared to the surrounding population.

Methods: This population-based historical cohort study included headache data from two large epidemiological surveys performed with an 11-year interval. This was linked with data from hospital records on exposure to head injury occurring between the health surveys. Participants in the surveys who had not been hospitalized because of a head injury comprised the control group. The head injuries were classified according to the Head Injury Severity Scale (HISS). Multinomial logistic regression was performed to investigate the association between head injury and new headache or exacerbation of pre-existing headache in a population with known pre-injury headache status, controlling for potential confounders.

Results: The exposed group consisted of 294 individuals and the control group of 25,662 individuals. In multivariate analyses, adjusting for age, sex, anxiety, depression, education level, smoking and alcohol use, mild head injury increased the risk of new onset headache suffering (OR 1.74, 95% CI 1.05–2.87), stable headache suffering (OR 1.70, 95% CI 1.15–2.50) and exacerbation of previously reported headache (OR 1.93, 95% CI 1.24–3.02). The reference category was participants without headache in both surveys.

Conclusion: Individuals hospitalized due to a head injury were more likely to have new onset and worsening of pre-existing headache and persistent headache, compared to the surrounding general population. The results support the entity of the ICHD-3 beta diagnosis "persistent headache attributed to traumatic injury to the head".

Keywords: Headache attributed to head injury, Head injury, Traumatic brain injury, Secondary headache disorders, Post-traumatic headache, Population-based

Background

Headache often has a major impact on the lives of the individuals affected, and constitutes a large social and economic burden for the global society [1–3].

Likewise, head injury is an important global health issue and a major cause of morbidity [4, 5]. Headache is the most frequent symptom following head injury, and it is manifested both as new onset and worsening of pre-existing headache [6–9]. The international classification of headache disorders (third edition, ICHD-3 beta) defines headache attributed to head injury (HAIH) as a headache with no defining clinical characteristics that starts within seven days of injury [10]. Persistent HAIH is of greater than 3 months' duration [10]. Long-term follow-up of headache after head injury entails methodological challenges. To investigate a causal relationship between head injury and subsequent headache, a control group for

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comparison is vital, preferably through a population-based design. There are, to our knowledge, only two other population-based, controlled studies on this subject and their findings are inconsistent [11, 12]. Moreover, both studies have methodological limitations [11, 12]. Headache prevalence and severity have been reported to be greater in those with mild head injury compared to those with more severe head injury [13, 14]. This inverse dose-response relationship is paradoxical and needs further investigation.

In a previous population-based historical cohort study, which was based on the third wave of the Nord-Trøndelag Health Study (HUNT), we evaluated the relationship between previous head injury and headache phenotype [15]. The primary aim of the current study was to analyze headache data for those who participated in both the second and third waves of the HUNT Study, evaluating the impact on new onset headache or exacerbation of headache due to head injuries in a population with known pre-injury headache status, taking into account the head injury severity.

Methods

Study design

This historical cohort study included data on headache from the second and third HUNT surveys, two large epidemiological surveys performed with an 11-year interval. Headache data was linked with data from hospital records on exposure to head injury occuring between the surveys. The exposed group consisted of study participants hospitalized due to a head injury, the remaining participants were used as controls.

The HUNT-surveys

The HUNT Study is a longitudinal cohort study in which all inhabitants ≥20 years of age in Nord-Trøndelag were invited to participate. Participants were examined three times. The two last surveys, HUNT2 (1995–1997) and HUNT3 (2006–2008) covered a large number of health-related items. Details of these comprehensive surveys, including non-respondents, are described elsewhere [16, 17].

Headache categories

Both HUNT2 and HUNT3 questionnaires included the screening question "Have you suffered from headache during the last 12 months?" The answers to the screening questions were used to categorize the responders into four mutually exclusive groups with regard to headache suffering at the two time points: Stable non-sufferers (headache-free in both studies), past sufferer (headache in HUNT2 but not in HUNT3), stable headache sufferer (headache in both studies) and new sufferer (headache in HUNT3, but not in HUNT2).

Participants answering "yes" to the headache screening question also reported their headache frequency. This enabled categorization of the responders with headache suffering in both surveys into three mutually exclusive groups: less frequent headache (in HUNT3 compared to HUNT2), stable headache frequency (same headache frequency in HUNT3 as in HUNT2), more frequent headache (in HUNT3 compared to HUNT2). Alternatives available for the headache frequency question were < 7, 7–14 and > 14 days/month.

To examine exacerbation or improvement in headache status between HUNT2 and HUNT3 we merged the frequency variable with the screening question so that each participant could be categorized in one of the following four groups: no headache suffering, headache suffering < 7 days/month, headache suffering 7–14 days/month, headache suffering > 14 days/month. Exacerbation of headache was defined as new onset of headache or increased frequency of previously reported headache. Improvement was defined as absence of or decrease in frequency of previously reported headache. Stable headache frequency was defined as headache suffering in both surveys with the same headache frequency in both.

Pre-existing headache was classified into two mutually exclusive groups: Migraine and non-migrainous headache. The approach used in determining headache subtype is described and validated elsewhere [18].

The validities of the headache questionnaires in HUNT2 and HUNT3 have been reported previously [18, 19]. For any headache suffering in HUNT2, the sensitivity was 85% and specificity 83% (kappa 0.57, 95% CI 0.41–0.73). For any headache suffering in HUNT3, the sensitivity was 88% and specificity 86% (kappa 0.70, 95% CI 0.61–0.79). A personal interview by a neurologist was used as gold standard.

Head injury data collection

All participants who had answered the headache screening question in HUNT3 and who had also been hospitalized in the region due to a head injury during the period 1988–2008 were identified in 2012 by a computer-based search. Details on how this was performed have been reported previously [15].

Information regarding the head injuries was collected from medical records. If the same individual had more than one head injury within the period, up to three of the most recent head injuries were recorded. The head injuries were classified according to the Head Injury Severity Scale (HISS) [20].

Only participants who answered the headache screening question in both HUNT2 and HUNT3 were of interest for analyses. Participants with head injuries between participation in HUNT2 and HUNT3 were included in

the exposed group. Participants with head injuries before HUNT2 were excluded.

Other measurements

The HUNT2 and HUNT3 surveys included many health-related items, and in the present study we used the following information about the participants in addition to headache status: age, sex, duration of education, smoking habits, total Hospital Anxiety and Depression Scale (HADS) score, self-reported health, BMI and CAGE score. The HADS is a fourteen item scale used to determine levels of anxiety and depression. The CAGE questionnaire is a widely used screening instrument for potential alcohol problems [21].

Statistical analysis

Demographic data for individuals with and without head injury are presented as means with standard deviations (continuous variables) and percentages (categorical data). In multivariate analyses, using multinomial logistic regression, we first examined the association between head injury and relative headache status in HUNT3 versus HUNT2 with regard only to suffering from headache and then the association between head injury and relative headache status in HUNT3 versus HUNT2 with regard both to suffering from headache and change in headache frequency. The results are presented as odds ratios (OR) with 95% confidence intervals (CI). OR's for which the 95% CI did not include 1 were considered statistically significant. Stable non-sufferers were used as reference category. The associations were investigated both with head injury as a binary variable (yes/no) and with head injury in four categories according to head injury severity (no head injury/minimal/mild/moderate head injury).

In the multivariate analyses we initially adjusted for age and sex. Subsequently, we also added the following potential confounding factors retrieved from the HUNT2 dataset: duration of education (≤ 9, 10–12 and ≥13 years) as proxy for socioeconomic status, daily smoking (yes/no), total HADS score (categorized from a continuous variable into three categories with score ≤ 16, 17–21 and ≥22) and CAGE score (0 or ≥1). In the logistic regression analyses missing data were handled by listwise deletion. Linearity of the continuous variables with respect to the logit of the dependent variable was assessed via the Box-Tidwell procedure [22]. The continuous variable age was found to fail the assumption of linearity and was split into categories with 10 year intervals. We investigated potential interactions between all covariates and head injury by including the product of the two variables into the multinomial logistic regression analyses. The interaction coefficients were tested using Wald statistics, with p-values less than 0.05 considered statistically significant. Because headache disorders in general are highly dependent on sex [17], separate analyses after stratifying for sex are common in research concerning headache. Consequently we chose to also do separate analyses after stratifying for sex. No formal adjustment for multiple testing was made.

The study was approved by the Regional Committee for Medical and Health Research Ethics and by the HUNT Research Centre.

Results

Participants

The flow of participants through the different stages of the study is presented in Fig. 1. A total of 294 participants had been hospitalized due to a head injury during the 11 year time period between the two surveys (exposed). The remaining 25,662 individuals were not hospitalized for head injury during this period (unexposed). Demographic data for the two groups are presented in Table 1. Prevalence of headache in HUNT2 was similar in the two groups (43.9% versus 41.7%, χ^2 (1) = 0.575, p = 0.45).

Head injuries

Among the 294 individuals with head injuries, 11 experienced two head injuries, adding up to a total of 305 incidents. Taking into account only the first head injury (of those with more than one), 11.9% of the head injuries were minimal, 71.8% were mild, 10.9% were moderate and 5.4% were unclassifiable. There were no severe head injuries. The most common injury mechanism was falling (55.1%), followed by traffic accidents (28.6%) and assault (1.7%).

A CT scan was performed in 56.4% (n = 172), an MRI in 1.0% (n = 3) and a plain X-ray of the head in 3.6% (n = 11) of the cases. The scans revealed traumatic pathology in 16.0% (n = 47). In total, 9.2% (n = 27) of all patients had intracranial pathology. 9.9% (n = 29) had cranial fractures (revealed either by imaging or clinical findings), and 5.1% (n = 15) had both cranial fracture and intracranial pathology.

Headache categories

Among the 25,956 partcipants, 12,830 (49.4%) were headache free in HUNT2 and HUNT3 (stable non-suffering), 6303 (24.3%) suffered from headache in both surveys (stable headache suffering), 4523 (17.4%) reported headache in HUNT2 only (past headache suffering) and 2300 participants (8.9%) had no headache in HUNT2, but reported to suffer from headache in HUNT3 (new headache suffering).

Among the 129 participants with head injury and pre-existing headache, 46 (35.7%) suffered from migraine, 57 (44.2%) from non-migrainous headache and 26 (20.2%) were unclassifiable.

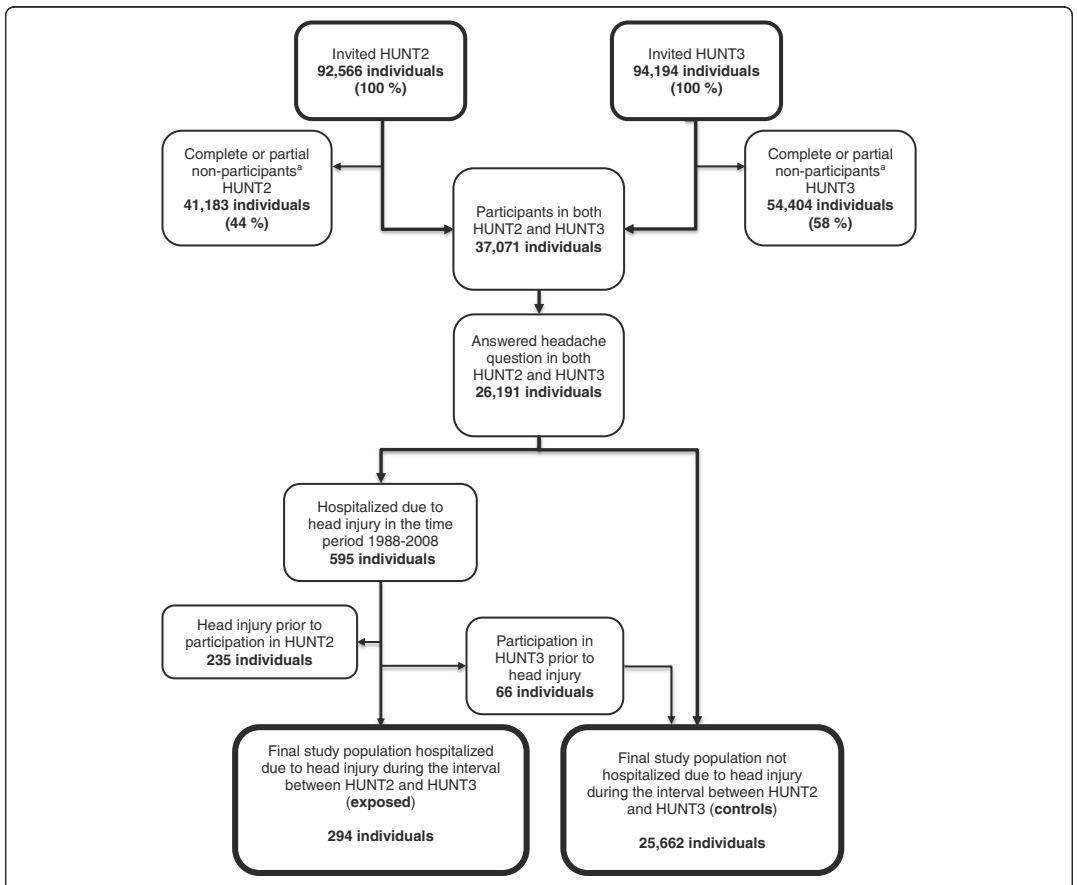

Fig. 1 Flow of participants through the HUNT2 and HUNT3 study and selection of head injury patients. [a]Complete non-participants: Answering no questionnaire. Partial non-participants: Answering part of the questinonnaire, but not the headache screening question. Abbreviations: HUNT = the Nord-Trøndelag Health Study

Individuals with mild head injury were more likely to have new onset of headache (OR 1.74, 95% CI 1.05–2.87) and stable headache suffering (OR 1.70, 95 CI 1.15–2.50) compared to controls (Table 2).

Table 3 demonstrates change in monthly headache frequency between HUNT2 and HUNT3 among participants suffering from headache in both surveys. In the head injury population 15.0% had more frequent headache in HUNT3 than in HUNT 2, in the control population the corresponding proportion was 12.2%.

There was a significant association between exacerbation of headache and head injury (Table 4). There was a nearly doubled odds of exacerbation of headache among those exposed to mild head injury than among the controls (OR 1.93, 95% CI 1.24–3.02) (Table 4). Individuals with head injury were also more likely to have stable headache suffering with unchanged frequency from HUNT2 to HUNT3 than the controls (Table 4). There was no significant relationship between moderate head injury and any of the headache trajectories (Tables 2 and 4).

There were no significant associations between head injury and past headache suffering or improvement of headache status.

No consistent significant interaction was observed between head injury and any of the covariates. The only significant interaction observed was for smoking and only in the case of improvement of headache.

Although no significant interaction was observed between sex and head injury, we did separate analyses for males and females for all headache trajectories. In these separate analyses, significant associations were found only for men (Tables 2 and 4).

Table 1 Demographics and health related variables

	Head injury population	Controls
Variable		
Total number of subjects	294	25,662
Age at participation in HUNT2 (years) (mean ± SD)	48.4 ± 14.7	47.3 ± 13.1
Age at injury (first injury) (years) (mean ± SD)	53.8 ± 15.2	
Age at participation in HUNT3 (years) (mean ± SD)	59.6 ± 14.7	58.5 ± 13.1
Time from head injury (first injury) to HUNT3 (years) (mean ± SD)	4.9 ± 3.2	
Female	137 (46.5)	14,639 (57.0)
Duration of education (HUNT2) (n (%))		
≤ 9 years	82 (27.9)	7535 (29.4)
10–12 years	135 (45.9)	11,663 (45.4)
≥ 13 years	73 (24.8)	6007 (23.4)
HADS score (mean ± SD) (HUNT2)	8.8 ± 5.7	7.4 ± 5.4
HADS score (mean ± SD) (HUNT3)	8.5 ± 6.0	7.3 ± 5.4
BMI (mean ± SD) (HUNT2)	26.2 ± 3.9	26.0 ± 3.6
BMI (mean ± SD) (HUNT3)	27.4 ± 4.3	27.4 ± 4.3
Daily smoking (HUNT2) (n (%))	62 (21.1)	6278 (24.5)
Daily and occasionally smoking (HUNT3) (n (%))	73 (24.8)	5338 (20.8)
Self-reported health poor or less than good (HUNT2) (n (%))	82 (27.9)	5451 (21.2)
Self-reported health poor or less than good (HUNT3) (n (%))	102 (34.7)	6883 (26.8)
Headache sufferer (n (%))		
HUNT2	129 (43.9)	10,697 (41.7)
HUNT3	111 (37.8)	8492 (33.1)
CAGE[a] ≥ 1 (HUNT2) (n (%))	56 (19.0)	3721 (14.5)
CAGE[a] ≥ 1 (HUNT3) (n (%))	58 (19.7)	3834 (14.9)

Abbreviations: *HADS* Hospital Anxiety and Depression Scale, *BMI* Body Mass Index
[a]*CAGE* Modified Norwegian version of the CAGE alcohol-screening instrument

Discussion

This is the first study which presents population based data on headache occurrence after head injury with known pre-injury headache status. Our main finding was that exposure to head injury increased the risk of new onset headache suffering and exacerbation of headache. Also, head injury was positively associated with stable headache suffering, which means that headache was less likely to improve. This confirms findings from several studies with less reliable study designs during the last years [9, 23, 24], but contrast with an earlier population-based study, which did not find an association between previous head injury and headache [12]. However, in that study there was a 22-year interval between the exposure to trauma and inquiry about headache [12].

The data were analyzed with regard to sex differences, since both prevalences of primary headache, as well as injuries to the head, are known to differ between men and women [25, 26]. The available literature concerning any sex-differences for persistent HAIH has been inconsistent [6, 27–29]. We did not find any significant difference between males and females in the effect of a head injury on change in headache status from HUNT2 to HUNT3. In the analyses stratified upon sex, the positive associations from the combined analysis were observed to be significant only among men. This could be an incidental finding.

Earlier studies have shown an inverse dose-response relationship between the severity of head injuries and development of persistent headache [13, 14]. In our analyses the estimated odds for all unfavourable headache trajectories after a mild head injury were higher than the corresponding odds found for moderate head injury. This indicates that although sequelae in general after mild head injuries are milder compared to more severe head injuries, patients with previous mild head injuries may be just as, or even more affected by headache. This seems to confirm the paradoxical finding in earlier studies of a lack of a positive dose-response relationship between head injury severity and HAIH. However, the present study included few moderate head injuries, which gives low power. Furthermore, the classification of head injury severity has differed widely, which makes comparisons between studies difficult [30–32].

Strengths

The major strengths of this study were the large population-based dataset on headache at two time points, combined with extensive objective information on each head injury, retrieved from medical records which eliminated recall bias regarding the head injury and enabled us to classify the head injuries according to severity. We had validated information about the headache status of the participants before the head injury, which enabled us to compare prevalence as well as frequency before and after the time of the head injuries and make comparisons with a non-exposed control group. This has not been possible in earlier studies. The design eliminates recall bias also regarding pre-study headache suffering, which can be a problem in prospective studies, as participants might tend to trivialise headache before the head injury because they understand their headache as a consequence of their head injury. Such possible under-reporting of pre-injury headache could be the reason why several prospective studies report pre-injury headache prevalence far below known headache prevalence in the general population [33–35]. This is especially a problem in studies without control groups. In some studies, using a control group

Table 2 Multivariate regression analyses of the associations between head injury and relative headache status in HUNT3 versus HUNT2 with regard to suffering from headache only

		All		Men	Women
		Adjustment for age and sex	Complete adjustment[a]	Complete adjustment[a]	Complete adjustment[a]
	N	N (OR, 95% CI)	N (OR, 95% CI)	N (OR, 95% CI)	N (OR, 95% CI)
Past headache suffering					
No head injury (reference)	25,662	4474 (ref.)	4474 (ref.)	1603 (ref.)	2871 (ref.)
Any head injury	294	49 (1.21, 0.87–1.69)	49 (1.23, 0.85–1.78)	24 (1.35, 0.82–2.21)	25 (1.06, 0.60–1.86)
Minimal head injury	35	7 (1.15, 0.47–2.80)	7 (0.94, 0.33–2.70)	1 (0.50, 0.06–4.14)	6 (1.17, 0.33–4.18)
Mild head injury	211	36 (1.35, 0.91–2.00)	36 (1.39, 0.89–2.15)	18 (1.53, 0.85–2.75)	18 (1.19, 0.61–2.32)
Moderate head injury	32	5 (1.13, 0.41–3.13)	5 (1.24, 0.43–3.54)	4 (1.41, 0.44–4.49)	1 (0.93, 0.08–10.52)
Stable headache suffering					
No head injury (reference)	25,662	6223 (ref.)	6223 (ref.)	1833 (ref.)	4390 (ref.)
Any head injury	294	80 (1.51, 1.13–2.03)	80 (1.55, 1.12–2.14)	37 (1.65, 1.06–2.56)	43 (1.37, 0.85–2.20)
Minimal head injury	35	10 (1.20, 0.53–2.70)	10 (0.96, 0.38–2.42)	4 (1.22, 0.32–4.60)	6 (0.78, 0.21–2.86)
Mild head injury	211	56 (1.60, 1.12–2.27)	56 (1.70, 1.15–2.50)	27 (1.91, 1.13–3.22)	29 (1.42, 0.80–2.51)
Moderate head injury	32	9 (1.58, 0.66–3.75)	9 (1.45, 0.57–3.70)	4 (0.90, 0.24–3.34)	5 (2.54, 0.45–14.30)
New headache suffering					
No head injury (reference)	25,662	2269 (ref.)	2269 (ref.)	974 (ref.)	1295 (ref.)
Any head injury	294	31 (1.44, 0.96–2.15)	31 (1.37, 0.88–2.15)	21 (1.89, 1.12–3.21)	10 (0.70, 0.29–1.69)
Minimal head injury	35	1 (0.33, 0.04–2.47)	1 (0.38, 0.05–2.90)	1 (0.81, 0.10–6.75)	0 (–)
Mild head injury	211	27 (1.86, 1.20–2.90)	27 (1.74, 1.05–2.87)	17 (2.31, 1.26–4.23)	10 (1.02, 0.41–2.52)
Moderate head injury	32	3 (1.20, 0.34–4.22)	3 (1.30, 0.36–4.65)	3 (1.75 (0.48–6.42)	0 (–)

One analysis was done with head injury as a binary variable (no head injury/any head injury) and a separate analysis was done with head injury in four categories according to head injury severity (no head injury/minimal head injury/mild head injury/moderate head injury). The head injury severity was classified according to the Head Injury Severity Scale (HISS)
Reference category: Stable non-sufferer (absence of headache suffering in both surveys)
Abbreviations: *OR* Odds ratio, *CI* Confidence interval
[a]Analyses are adjusted for age, sex, duration of education, daily smoking, CAGE score ≥ 1 and HADS-score

Table 3 Change in monthly headache frequency between HUNT2 and HUNT3 among participants suffering from headache in both surveys

HUNT2	HUNT3	N (%), head injury population	N (%), controls
Decreased headache frequency[a]		10 (12.5)	939 (15.1)
> 14 days	1–14 days	2 (2.5)	269 (4.3)
7–14 days	< 7 days	8 (10.0)	670 (10.8)
Stable headache frequency[b]		55 (68.8)	4234 (68.0)
< 7 days	< 7 days	46 (57.5)	3833 (61.6)
7–14 days	7–14 days	4 (5.0)	257 (4.1)
> 14 days	> 14 days	5 (6.3)	144 (2.3)
Increased headache frequency[c]		12 (15.0)	757 (12.2)
< 7 days	7–30 days	10 (12.5)	633 (10.2)
7–14 days	> 14 days	2 (2.5)	124 (2.0)
Missing		3 (3.8)	293 (4.7)
Total		80 (100.0)	6223 (100.0)

[a]Less frequent headache (days/month) in HUNT3 compared to HUNT2
[b]Same headache frequency (days/month) in HUNT3 as in HUNT2
[c]More frequent headache (days/month) in HUNT3 compared to HUNT2

with injuries other than head injuries could be an advantage, as one could theorize that physical trauma could cause headache through psychosocial stressors, regardless of which part of the body is injured. However, if the study is epidemiological, the design is population-based and the intention is to investigate whether head injury is a risk factor for development of headache regardless of the underlying mechanism, a community control group is more appropriate [36].

In a previous study, we analysed headache in HUNT3 related to all hospitalized head injuries ($n = 940$) between 1988 and HUNT3 [15]. As in the present study, there was a significant association between head injury and headache. However, in that study we were not able to take headache status before the trauma into account. This was a limitation because in patients with headache complaints a trauma may cause stress which can precipitate an attack of their pre-existing headache. Headache in a trauma setting can be a sign of a serious head injury, and these patients may therefore be referred to a hospital. Hence, one could imagine that pre-existing headache could act as a confounder. However, the present

Table 4 Multivariate regression analyses of the associations between head injury and relative headache status in HUNT3 versus HUNT2 with regard both to suffering from headache as well as to change in headache frequency

		All		Men	Women
		Adjustment for age and sex	Complete adjustment[a]	Complete adjustment[a]	Complete adjustment[a]
	N	N (OR, 95% CI)	N (OR, 95% CI)	N (OR, 95% CI)	N (OR, 95% CI)
Improvement of headache status[1]					
No head injury (reference)	25,662	5413 (ref.)	5413 (ref.)	1852 (ref.)	3561 (ref.)
Any head injury	294	59 (1.22, 0.89–1.68)	59 (1.21, 0.85–1,72)	28 (1.30, 0.81–2.08)	31 (1.06, 0.63–1.80)
Minimal head injury	35	12 (1.62, 0.76–3.44)	12 (1.35, 0.56–3.24)	2 (0.76, 0.15–3.82)	10 (1.65, 0.54–4.98)
Mild head injury	211	40 (1.26, 0.86–1.84)	40 (1.27, 0.83–1.95)	20 (1.39, 0.79–2.47)	20 (1.09, 0.58–2.07)
Moderate head injury	32	6 (1.16, 0.44–3.02	6 (1.23, 0.45–3.31)	5 (1.51, 0.51–4.42)	1 (0.66, 0.06–7.63)
Stable headache suffering and frequency[2]					
No head injury (reference)	25,662	4234 (ref.)	4234 (ref.)	1302 (ref.)	2932 (ref.)
Any head injury	294	55 (1.55, 1.11–2.15)	55 (1.60, 1.12–2.28)	28 (1.86, 1.16–2.99)	27 (1.30, 0.76–2.21)
Minimal head injury	35	5 (0.88, 0.32–2.45)	5 (0.71, 0.23–2.25)	3 (1.37, 0.33–5.68)	2 (0.28, 0.03–2.39)
Mild head injury	211	40 (1.71, 1.15–2.53)	40 (1.83, 1.20–2.79)	20 (2.14, 1.22–3.76)	20 (1.48, 0.79–2.77)
Moderate head injury	32	5 (1.26, 0.44–3.61)	5 (1.06, 0.33–3.40)	3 (0.87, 0.19–4.02)	2 (1.40, 0.18–10.82)
Exacerbation of headache status[3]					
No head injury (reference)	25,662	3026 (ref.)	3026 (ref.)	1181 (ref.)	1845 (ref.)
Any head injury	294	43 (1.55, 1.09–2.21)	43 (1.52, 1.02–2.25)	26 (1.87, 1.14–3.05)	17 (1.08, 0.56–2.08)
Minimal head injury	35	1 (0.24, 0.03–1.83)	1 (0.26, 0.03–2.03)	1 (0.62, 0.07–5.16)	0 (–)
Mild head injury	211	37 (2.00, 1.35–2.98)	37 (1.93, 1.24–3.02)	22 (2.40, 1.37–4.21)	15 (1.37, 0.66–2.85)
Moderate head injury	32	5 (1.56, 0.55–4.41)	5 (1.65, 0.57–4.79)	3 (1.42, 0.39–5.22)	2 (2.09, 0.27–16.16)

One analysis was done with head injury as a binary variable (no head injury/any head injury) and a separate analysis was done with head injury in four categories according to head injury severity (no head injury/minimal head injury/mild head injury/moderate head injury). The head injury severity was classified according to the Head Injury Severity Scale (HISS)
Reference category: Stable non-sufferer (absence of headache suffering in both surveys)
Abbreviations: *OR* Odds ratio, *CI* Confidence interval
[1]Improvement of headache status: Absence of previously reported headache or decrease in its frequency
[2]Stable headache suffering and frequency: Headache suffering in both HUNT2 and HUNT3 with the same frequency in both studies
[3]Exacerbation of headache status: New onset of headache or increased frequency of previously reported headache
[a]Analyses are adjusted for age, sex, duration of education, daily smoking, CAGE score ≥ 1 and HADS-score

study shows that in the head injury group pre-existing headache was not more prevalent than in the control group, while new headache and exacerbation of headache was. We therefore find no reason to suspect the occurrence of such confounding.

Limitations

The study was not designed to determine time of headache onset. Therefore, we cannot specify if the onset of headache was within 7 days after head injury, which is a criterion for classifying a headache as HAIH, according to ICHD-3 beta [10]. However, ICHD-3 beta states that this criterion is somewhat arbitrary and concludes further research is needed into which interval might be more appropriate [10].

The present study included only 32 individuals with a moderate and 35 individuals with a minimal head injury, which gives low power and uncertain results from these groups. Furthermore, generalization of results should be performed with caution, since only 56% of those invited to participate in HUNT2 and 42% of those invited to participate in HUNT3 answered the headache questionnaire.

Patients not examined at a hospital were not included. However, the proportion of patients with head injury being admitted to a hospital after examination by health care providers was larger in the period of data collection than it is today [26, 37]. This can mostly be attributed to increased availability of CT imaging and the implementation of guidelines for initial management of head injury in Norwegian hospitals [38].

Implications for public health

HAIH is one of the most prevalent of secondary headaches worldwide and a potentially preventable one. Everywhere, but especially in low and middle-income countries, head injury is common and most often caused by road traffic injuries, falls and violence [39]. An important step in reducing the incidence of HAIH is therefore head injury preventive strategies [39].

The fact that development of HAIH also, or even especially, occurs after mild head injuries should have implications for the follow-up of patients with mild head injury. In Norway, like many other countries, there are no guidelines for follow-up after mild head injury. We know little about individual factors that predispose to development of persistent HAIH. We therefore suggest that all persons seeking medical advice due to a mild head injury should be encouraged to seek their general practitioner in the case of development of new headache or exacerbation of already existing headache with a duration longer than 3 months. A recent study suggests that a standardized tool might be helpful in the general population of concussion patients to assess for post-traumatic headache [40]. While we await better knowledge of how to best treat HAIH, we suggest using treatment strategies with proven efficacy against the primary headache that it most resembles [41].

Future research

The incidence of mild head injury is high and a close follow-up of all persons experiencing a mild head injury would require a large effort for the health care service. It is therefore especially important to be able to identify persons at risk of developing HAIH and develop clinical guidelines for follow-up after mild head injury. HAIH occurred more frequently in patients with minimal traumatic intracranial haemorrhage after mild TBI than those without in a recent published study [42]. Another study found that persistent HAIH and migraine are associated with differences in brain structure [43]. Both studies suggests that it is possible to find underlying pathophysiology that separates HAIH from the primary headache type it phenotypically resembles. Future research should be aimed at understanding its pathophysiological mechanisms, acquiring knowledge on predictors for development of HAIH and based on this, develop effective preventive measures and treatment options.

Conclusion

Individuals hospitalized due to a mild head injury were more likely to develop new headache suffering or report exacerbation of previously documented headache compared to the surrounding general population. Hence, the present study substantiates HAIH as a true secondary headache entity and not a primary headache misattributed to head injury.

Abbreviations

BMI: Body Mass Index; CAGE: Modified Norwegian version of the CAGE alcohol-screening instrument; CI: Confidence Interval; HADS: Hospital Anxiety and Depression Scale; HAIH: Headache Attributed to Head Injury; HISS: Head Injury Severity Scale; HUNT: the Nord-Trøndelag Health Study; ICD: International Classification of Diseases; ICHD-3 beta: the International Classification of Headache Disorders, beta version of third edition; OR: Odds Ratio

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Availability of data and materials

Part of the dataset supporting the conclusions of this article is available on request to the corresponding author. Some of the data are the property of HUNT research centre and can only be accessed through direct contact with the research centre.

Authors' contributions

LHN, study concept and design, acquisition of data, analysis and interpretation of data, writing of manuscript. KH, analysis and interpretation of data, critical revision of manuscript for intellectual content. AV, study supervision, interpretation of data, critical revision of manuscript for intellectual content. LJS, study concept, interpretation of data, critical revision of manuscript for intellectual content. TF, analysis and interpretation of data, critical revision of manuscript for intellectual content. TP, acquisition of data, critical revision of manuscript for intellectual content. GBG, acquisition of data, critical revision of manuscript for intellectual content. ML, study concept and design, organizing retrieval of data, study supervision, interpretation of data, critical revision of manuscript for intellectual content. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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Paper III