Primary recurrent headaches among adolescents

Prevalence and risk factors

by

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Tønsberg, June 2015

Brit Andenes Blaauw
### ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>CBCL</td>
<td>Child Behavior Check List</td>
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<tr>
<td>DSM</td>
<td>Diagnostic and Statistical Manual of Mental Disorders</td>
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<td>HUNT</td>
<td>Helseundersøkelsen i Nord-Trøndelag (The Nord-Trøndelag health study)</td>
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<td>ICD-10</td>
<td>International Classification of Diseases, 10th revision</td>
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<tr>
<td>ICHD-1</td>
<td>The first edition of the International Classification of Headache Disorders (1988)</td>
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<tr>
<td>ICHD-3</td>
<td>The third edition of the International Classification of Headache Disorders (2013)</td>
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<td>IHS</td>
<td>International Headache Society</td>
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<td>MI</td>
<td>Migraine</td>
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<td>NCH</td>
<td>Non-classifiable headache</td>
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<td>OR</td>
<td>Odds Ratio</td>
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<tr>
<td>SCL</td>
<td>Symptom Check List</td>
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<tr>
<td>TTH</td>
<td>Tension-type headache</td>
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<td>WHO</td>
<td>World Health Organization</td>
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SUMMARY IN ENGLISH

**Background:** Epidemiological studies have shown that headaches in general, and recurrent primary headache disorders such as migraine (MI) and tension-type headache (TTH) in particular, are common complaints among adolescents, especially girls. Increasingly, headaches are being recognized as a significant health problem in this age group. They can significantly disable adolescents by affecting their daily lives, performance in school and social activities. Increased knowledge about the epidemiology of headache among adolescents is needed, but currently, most studies are done on adults. Assessment of co-morbid disorders and recognition of risk factors is required in order to improve the management of adolescents with recurrent headaches.

**Purpose:** In the present study, the aim was to assess change in the prevalence of primary headaches among adolescents over a four-year period. We also wanted to assess the relationships between symptoms of anxiety and depression, conduct and attention difficulties and recurrent headaches in a large-scale epidemiological study of adolescents and in a follow-up study four years later.

**Material and methods:** This thesis is based on three separate articles (Papers I-III). Two cross-sectional, population-based studies were conducted in Norway, one from 1995 to 1997 (Young-HUNT1), and the other from 1999 to 2001 (Young-HUNT2). In Young-HUNT1, 5838 adolescents aged 12 to 20 years were interviewed about their headache complaints and completed a comprehensive questionnaire that included symptoms of anxiety and depression and behavioral problems, i.e. conduct and attention difficulties. All students in 2nd and 3rd grade of upper secondary school (aged 16 to 20 years) and all apprentices of the same age who participated in Young-HUNT1 were invited to take part in Young-HUNT2. This study was performed exactly as the earlier study, with 1665 participants answering the same questionnaire and headache interview. In Paper I, the prevalence of primary headaches among Norwegian adolescents aged 16–20 years in two periods were compared. In Paper II, we assessed the relationship of symptoms of anxiety and depression and behavioral problems with primary headaches based on data from Young-HUNT1. Paper III investigates the
influence of symptoms of anxiety and depression and behavioral problems at baseline, on recurrent headaches at follow-up four years later.

**Results: Paper I** showed that the overall prevalence of recurrent headaches increased significantly from Young-HUNT1 to Young-HUNT2. An increase was seen in all types of recurrent headache, and was significant for TTH. In **Paper II**, symptoms of anxiety and depression and behavioral problems were associated with recurrent headaches. MI was significantly associated with symptoms of anxiety and depression and attention difficulties, but not with conduct difficulties. TTH was significantly associated only with symptoms of anxiety and depression. Non-classifiable headache (NCH) was associated with anxiety and depression as well as attention and conduct difficulties. **Paper III** showed that symptoms of anxiety and depression in early adolescence were associated with recurrent headaches four years later. This association was evident for MI and NCH, but was not statistically significant for TTH. Among adolescents without headaches at baseline, symptoms of anxiety and depression were associated with new onset MI four years later and attention difficulties were associated with new onset NCH. We found no associations between anxiety and depression or behavioral problems at baseline and new-onset TTH at follow-up.

**Conclusions:** Earlier follow-up studies have examined changes in the prevalence of recurrent headaches in youth, but the results are divergent. Our findings support the impression that the prevalence of recurrent headaches among adolescents is increasing, and underlines the need for prospective designed studies with emphasis on prognosis and etiological factors. Both symptoms of anxiety and depression and behavioral problems were associated with recurrent headaches. Recognizing and identifying these associated factors should be considered part of the clinical assessment of young headache patients, and addressing them in interventions may improve headache management.
**SUMMARY IN NORWEGIAN (SAMMENDRAG PÅ NORSK)**

**Bakgrunn:** Epidemiologiske studier har vist at hodepine og spesielt tilbakevendende primær hodepine som migrrene og tensjonshodepine er vanlig hos ungdom, særlig jenter. Hodepine blir i økende grad oppfattet som et helseproblem i denne aldersgruppen og kan føre til omfattende handikap ved å påvirke ungdommenes liv, skole prestasjoner og sosiale aktiviteter. Det er behov for økt kunnskap omkring hodepine epidemiologi hos ungdom siden de fleste studier er gjort på voksne. Undersøkelse av komorbide tilstander og identifisering av risikofaktorer er viktig for å kunne ta bedre hånd om ungdom med tilbakevendende hodepine.

**Hensikt:** I denne studien var målet å se om prevalensen av primær hodepine hos ungdom hadde endret seg over en fire års periode. Vi ville også undersøke sammenhengen mellom hodepine og symptomer på angst og depresjon, atferdsvansker og oppmerksomhetsproblemer i en stor befolkningsundersøkelse blant ungdom samt i en oppfølgingsundersøkelse fire år senere.

**Materiale og metode:** Denne avhandlingen er basert på tre separate artikler (**Paper I-III**). I perioden 1995-1997 (Ung-HUNT1) og 1999-2001 (Ung-HUNT2) ble det utført to befolkningsbaserte tversnittsundersøkelser i Nord-Trøndelag. I Ung-HUNT1 fullførte 5838 ungdom i alderen 12 til 20 år et omfattende spørreskjema som inkluderte symptomer på angst eller depresjon, atferdsvansker og oppmerksomhetsproblemer, og de ble intervjuet om sine hodepine plager. Alle elever i 2. og 3. klasse på videregående skole (16-20 år) og alle læringer i samme alder som hadde deltatt i Ung-HUNT1 ble invitert til Ung-HUNT2. Denne studien ble utført på eksakt samme måte som den tidligere studien og 1665 deltok andre svarte på det samme spørreskjemaet og gjennomgikk et identisk hodepine intervju. I **Paper I** sammenlignet vi prevalensen av hodepine hos ungdom i alderen 16-20 år i de to periodene. Sammenhengen mellom symptomer på angst eller depresjon, atferdsvansker og oppmerksomhetsproblemer i Ung-HUNT1 ble undersøkt i **Paper II.** I **Paper III** undersøkte vi effekten av symptomer på angst eller depresjon, atferdsvansker og oppmerksomhetsproblemer i Ung-HUNT1 i
relasjon til tilbakevendende hodepine ved oppfølgingsundersøkelsen (Ung-HUNT2) fire år senere.


LIST OF PUBLICATIONS

The present thesis is based on the following papers, referred to in the text by their Roman numerals:


   The Nord-Trøndelag Health Study shows increased prevalence of primary recurrent headaches among adolescents over a four-year period.


   Anxiety, depression and behavioral problems among adolescents with recurrent headache: the Young-HUNT study.


   The relationship of anxiety, depression and behavioral problems with recurrent headache in late adolescence – a Young-HUNT follow-up study.

   *The Journal of Headache and Pain 2015;16:10*
1 INTRODUCTION

Earlier epidemiological studies have shown that headaches in general, and recurrent primary headache disorders in particular, are common complaints among adolescents (1-4). MI and TTH are the most frequently reported types of primary headaches with prevalence rates of approximately 10% for MI and 15-20% for TTH in population-based studies (5-7) and it is uncertain whether the prevalence is increasing (8). Increasingly, headaches are being recognized as a significant health problem among adolescents, which affect their daily lives, including school performances and social activities (9, 10).

Epidemiologic studies have contributed greatly in revealing important pathological mechanisms, triggers and risk factors for headaches. However, the fundamental causes and mechanisms of the primary headaches are still uncertain (11-13). Earlier follow-up studies have examined changes in prevalence of recurrent headaches among children and adolescents, but the results are divergent (14-16). Reliable information about changes in prevalence of primary headaches over a period of time is important both from a clinical, and a public health, perspective. Assessment of comorbid disorders is also needed to improve management of adolescents with recurrent headaches. In various studies, MI has been found to be comorbid with a number of diseases. The comorbidity of other headache forms is far less studied (17-20). The association between headaches and psychiatric symptoms is well documented, but there is limited knowledge of their possible connection with anxiety and depression as well as behavioral problems among adolescents (21).

In this thesis, different aspects of primary recurrent headaches among adolescents are investigated. The aims were to examine changes in headache prevalence over a four-year period and to explore the association of recurrent headaches with symptoms of anxiety and depression as well as with behavioral problems. We used data from the Young-HUNT Study, the adolescent part of the Nord-Trøndelag Health study (HUNT Study), including participants aged 12-20 years. In the present work, primary recurrent headaches have been studied in two cross-sectional studies within the same population. Headache diagnoses were derived from a headache interview performed by trained nurses in connection with a clinical examination at the schools during school hours. The diagnoses were made according to the diagnostic criteria from the International
Headache Society (IHS): The International Classification of Headache Disorders (ICHD-I) (22). The other variables were derived from a comprehensive self-administered questionnaire completed during one school hour. This thesis is based on three papers, all published and peer-reviewed in international journals.
2 BACKGROUND

2.1 Headache diagnoses and classification

Headache is a subjective complaint and the diagnosis is made on the basis of subjective experiences. There are no laboratory tests or objective measures to diagnose primary headaches. Headache diagnoses are, ultimately, dependent on self-report. This means that the way in which the headache interview is conducted, and the symptoms recorded, is important. Uniform diagnostic criteria are essential, not only for case definition, but also for the comparability of headaches within clinics and studies and around the world. The prevalence of a headache disorder depends on the criteria applied. Also, the formulation of questions in interviews and questionnaires, and the manner in which an interviewer presents them, has an impact on the prevalence (23). The use of a neutral question (“Do you have headaches?”) is shown to give higher prevalence rates than the use of questions involving some specification of the headaches’ severity (“Do you suffer from headaches?” or “Do you have severe headaches?”) (24).

2.1.1 The classification of headache disorders

The first diagnostic criteria for headaches were presented in 1962, when they were published by an Ad hoc committee of the National Institutes of Health. These original criteria were imprecise and incomplete. In 1988, IHS published a classification system that became standard for headache diagnoses: Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain (ICHD-I) (22). In 2004, a second edition was published: The International Classification of Headache Disorders (ICHD-II) (25, 26), with some criteria being later revised (27, 28). In 2013, the third edition was published (ICHD-III) (29).

The ICHD-I and II classify headaches as primary or secondary. ICHD-III uses three main categories: “the primary headaches”, “the secondary headaches” and “painful cranial neuropathies, other facial pains and other headaches”. The systems are hierarchical and contain major groups of headache disorders, which are subdivided up to three times into headache entities, subtypes and subforms. The principles have been incorporated into the International Classification of Diseases (ICD-10)(30). When widely used classification systems and their diagnostic criteria change markedly, the knowledge
acquired using the earlier criteria is of uncertain validity for disorders diagnosed with the revised criteria. As a consequence, it is possible that much research would have to be repeated. Fortunately, the first edition’s diagnostic criteria for the most important headache disorders remains undisputed and the criteria for MI and TTH have been preserved (31).

The “gold standard” method for diagnosing headaches is a combination of clinical interviews and examination performed by a neurologist using the diagnostic criteria. However, this approach is expensive and has only been used in a few population studies (32, 33). Screening by other health personnel (nurses, medical students) has been shown to be accurate when the aim is to identify the most common forms of primary headaches like MI and TTH (34). A recognition-based method, giving the participants descriptions of MI and TTH based on the IHS criteria, is a reliable tool for mass screening among adolescents (35), and has been applied in the present work.

2.1.2 Clinical features and classification of migraine

The two most common forms of MI are MI without aura and MI with aura. A typical MI attack progresses through three or four phases (36) (Figure 1). Hours to a day before the attack starts, many patients report vague symptoms collectively termed the premonitory phase (37). These symptoms may include fatigue, difficulty concentrating, stiffness in the neck, increased emotionality, or a general hypersensitivity to sensory stimuli. In about one third of MI patients specific neurological symptoms occur prior to, or overlapping with, the headache phase (16). This is known as the aura phase and normally lasts less than an hour. MI aura almost invariably starts with visual symptoms. Other common aura symptoms are sensory, such as numbness or pins and needles in the hand, arm and face, or difficulties with speech (aphasia) (38). Many patients experiences attacks both with and without aura. The subsequent headache phase is typically characterized by a unilateral throbbing headache, aggravated by physical activity, and accompanied by nausea, vomiting and aversion to light and sounds (25). Many patients prefer to lie down in a dark room, and avoid loud sounds or strong smells. Untreated, this phase normally lasts 4-72 hours. Finally, in the postdromal phase, most patients report vague symptoms similar to those described for the premonitory phase. These
may include fatigue, cognitive difficulties or an altered mood (36), and can last hours to days after the resolution of the headache.

**Figure 1. Typical sequence of a migraine attack**

![Migraine Attack Sequence](image)

Most MI patients can describe specific factors that may trigger a MI attack. Common triggers include stress, menstruation, reflected sunlight, lack of sleep or food, red wine, or specific perfumes or odors (39, 40) However, as most studies of MI triggers have been retrospective, it is possible that some of the reported triggers are a (25) consequence of the premonitory phase rather than actual triggers (36).

In the classification system, MI is divided into two major subtypes. MI without aura is a clinical syndrome characterized by headache with specific features and associated symptoms. MI with aura is primarily characterized by the transient focal neurological symptoms that usually precede, or sometimes accompany, the headache (25, 29).

### 2.1.3 Clinical features and classification of tension-type headache

TTH is characterized by a bilateral pressing tightness that occurs anywhere on the cranium or suboccipital region. The headache is typically frontal, although band-like, or temporal, pain can occur, which is sometimes described as a pressure or band around the head. The intensity is mild to moderate and the headache lasts from 30 minutes to several days. The pain is usually described as a continuous pressure although the intensity may vary. There may be associated photophobia or phonophobia, although these occur less often than with MI. It is not accompanied with nausea or vomiting nor aggravated by routine physical activity. Light-headedness and fatigue may occur (41, 42). The overlap of some of these symptoms with those of MI can make differentiation between the two headache types difficult, especially in children and adolescents (43, 44). The current classification distinguishes between three subforms of TTH; infrequent
episodic, frequent episodic and chronic (29), whereas ICHD-I distinguished between only episodic and chronic TTH (22). The signs and symptoms of infrequent, frequent and chronic TTH are similar and the diagnostic criteria are based more upon what TTH is not: localized, throbbing, severe or aggravated by activity.

2.1.4 Headache classification in children and adolescents

Introduction of the IHS criteria has improved the sensitivity and specificity of headache diagnosis (22). However, headaches in children differ from that in the adult population and the ability to describe and conceptualize pain is also age related (35). As children age, their descriptions and understanding of pain and headaches becomes more complex (45). Hence the applicability of the IHS criteria to children and adolescents has been debated (46-49). Some revisions in the diagnostic criteria for MI in children were accepted in the ICHD–II, which increased the difference between the criteria for children and for adults (25). The revisions included briefer MI attacks in children – 1 hour, compared to 4 hours for adults; either unilateral or bifrontal or bitemporal location, instead of only unilateral in adults; photo- or phonophobia, instead of photo- and phonophobia for adults. There were no revisions of diagnostic criteria for TTH in the ICHD–II, despite some suggestions, i.e. three, not two, out of four items to be required for criterion C, as well as to have no photophobia and phonophobia. The recommended new criteria were not accepted because its high specificity, but low sensitivity (25, 50). The diagnostic criteria for MI and TTH, according to IHS (modified from ICHD-I), are shown in Table 1.
Table 1. Diagnostic criteria for migraine and TTH according to IHS

Migraine
A. At least 5 attacks fulfilling B-D
B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)
C. Headache has at least two of the following characteristics:
   a. Unilateral location
   b. Pulsating quality
   c. Moderate or severe intensity (inhibits or prohibits daily activities)
   d. Aggravation by walking stairs or similar routine physical activity
D. During headache at least one of the following:
   a. Nausea and/or vomiting
   b. Photophobia or phonophobia
E. Not attributed to another disorder

Tension-type headache
A. At least 10 previous headache episodes fulfilling criteria B-D listed below
B. Headache lasting from 30 minutes to 7 days
C. At least 2 of the following pain characteristics:
   a. Pressing/tightening (non-pulsating) quality
   b. Mild or moderate intensity (may inhibit, but does not prohibit activities)
   c. Bilateral location
   d. No aggravation by walking stairs or similar routine physical activity
D. Both of the following:
   a. No nausea or vomiting (anorexia may occur)
   b. Photophobia and phonophobia are absent, or one but not the other is present
E. Not attributed to another disorder
2.2 Epidemiology and study designs

2.2.1 Epidemiology
Epidemiology means "the study of what is upon the people", and is derived from the Greek words: *epi* “upon, among”, *demos* “people” and *logos* "study". According to the World Health Organization (WHO), epidemiology is the study of the distribution and determinants of health-related states or events (including disease), and the application of this study to the control of diseases and other health problems (51). John Snow is known as the father of modern epidemiology because of his investigations into the causes of the 19th century cholera epidemics in London. He noticed the significantly higher death rates in two areas supplied with water by the Southwark Company. His identification of the Broad Street pump as the source of the Soho epidemic is considered the classic example of epidemiology (52). In the early 20th century, mathematical methods were introduced into epidemiology and several large-scale epidemiologic studies initiated in the 1940s have had far-reaching influences on healthcare. For example, the community-intervention trials on fluoride supplementation in water led to widespread prevention of dental caries (53) and The Framingham Heart Study contributed significantly to understanding the causes of cardiovascular disease (54). In the early 1950s, prospective epidemiological case-control studies led by Richard Doll and Austin Bradford Hill, lent very strong statistical support to the suspicion that tobacco smoking is linked to lung cancer (55, 56). The understanding and synthesis of epidemiologic concepts grew rapidly in the last third of the 20th century and evidence indicates that epidemiology is still in an early stage of its development (57). This explosion of epidemiologic activity has accentuated the need to improve understanding of its theoretical underpinnings. Epidemiology is a wide field and contains many different types of studies, all with strengths and weaknesses that one should bear in mind when evaluating research results and their interpretation (58, 59)

2.2.2 Epidemiological study designs
There are two main categories of study types within epidemiology: observational studies and experimental studies. In observational studies, information about groups of subjects is collected, but nothing is done to affect them. Experimental studies are those in which the researcher affects (controls) what happens to all, or some, of the
individuals, for example, through exposure to different treatments or agents. Observational studies can be divided into cross-sectional and longitudinal studies. Each study design has its own advantages, disadvantages and likelihood of errors (60).

**Cross-sectional design**

Cross-sectional studies are carried out at one time point or over a short period. The purpose of these studies is descriptive, and the aim is to describe a population, or a subgroup within the population, with respect to an outcome (effect) and a set of risk factors (exposures). They are relatively inexpensive, quick to perform and allow for the assessment of many outcomes and risk factors. This design is suitable for studying prevalence of disease and occurrence of exposure at the time the study is performed, like a snapshot of the current situation. They are useful for understanding disease etiology and for the generation of hypotheses, but are regarded as unsuitable for studying causality (61, 62). Repeated cross-sectional studies may be carried out to give a pseudolongitudinal study, in which the individuals in the study are chosen either from the same sampling frame or from a different one. Data from repeated cross-sectional surveys using independent random samples with standardized definitions and survey methods, provides useful indications of trends (61). Cross-sectional, or prevalence studies, are commonly used in headache epidemiology (63), including Paper I and Paper II in this thesis.

**Longitudinal design**

Examples of longitudinal studies are case-control and cohort studies, which can be retrospective (the investigator starts with the disease and works back to a possible cause) or prospective (61, 62).

In case-control studies, a group of patients (e.g. headache sufferers) is compared with a control group (healthy controls or controls with another disease). This study design is time and cost efficient and particularly well suited for the evaluation of rare diseases. A wide range of potential etiologic exposures can be effectively evaluated (64). Case-control studies can be used to test specific hypotheses and to explore possible exposures among affected and non-affected individuals. The major weakness of retrospective
studies is that both the exposure and disease have already occurred at the time of inclusion, making them susceptible to selection bias and recall bias (61, 64).

In a prospective observational longitudinal study subjects are followed over time, with continuous or repeated monitoring of risk factors and/or health outcomes. If repeated monitoring is done with over time, cross-sectional analyses can also be made using data from each of the sampling times. The follow-up of a cohort is a longitudinal study that can provide valuable information on the time-course and prognosis of a disease or follow the development of risk factors (65). The strength of prospective cohort studies is that exposure is measured prior to the onset of illness, making it possible to elucidate the temporal relationship between exposure and disease and minimize bias in the ascertainment of exposure. This study design is not suitable for investigating rare diseases, but is of special value when exposure is rare (61). In this work we have applied prospective cohort design in Paper III, by repeating the cross-sectional study in the same population four years later.

2.2.3 Headache epidemiology
Since the 1970s, headache studies have increased in number and relevance for clinical practice as a consequence of improved classification of headache disorders. Until 1988, and the first edition of the diagnostic criteria (ICHD-I), comparison between studies was difficult. More recent studies could provide new insight into headache epidemiology and have contributed greatly by revealing important pathological mechanisms, triggers and risk factors for headaches. However, the fundamental causes and mechanisms of the primary headaches are still uncertain (12, 13, 66-68). Hopefully, further epidemiologic studies will increase the knowledge of risk factors and ultimately provide clues concerning preventive strategies and mechanisms of disease.

Headaches are highly prevalent disorders affecting approximately 50% of the adult population each year (24, 69). There is an increased awareness of headaches as a major public health problem as several of its subtypes – TTH, MI, cluster headache and chronic daily headache – cause substantial levels of disability (70). MI and TTH are the most frequently reported types of primary headaches with prevalence rates of approximately
15% for MI and >60% for TTH among adults, and 10% and 15-20%, respectively, among children and adolescents (69, 71-74). Even though it is more common, TTH has not been extensively investigated in epidemiologic studies, whereas many studies have been performed on MI. However, because of its high prevalence, the social burden of TTH is probably as large as that of MI (70). Although prevalence rates of MI and TTH are lower among adolescents than adults, headaches are increasingly being recognized as a significant health problem in this age group and can lead to significant disabilities by affecting their daily lives, school performance and social activities (9, 10, 75, 76).

Migraine
The prevalence of MI changes markedly with age (Figure 2). In early life the prevalence is low, with about 4% of school children being affected, boys and girls equally (77). Throughout adolescence the prevalence in boys remains stable while it increases among girls. The prevalence increases rapidly from around the time of puberty, with most patients having their first attack in their second or third decade. The prevalence peaks around the fourth decade, coinciding with the most productive period of life (19, 78, 79). In adulthood, MI is two to three times more common in women than in men (69, 71, 80). Around the time of menopause the prevalence falls rapidly (19, 81).

Figure 2. Migraine prevalence in relation to age in men and women in Europe. Adapted from Stovner et. Al. 2006. Used with permission.

Several follow-up studies among adolescents have shown relatively stable prevalence rates of MI (16, 72, 82, 83). A review of epidemiological studies on MI among children
and adolescents ≤20 years in the period of 1988 to 2013 showed an overall mean prevalence of MI of 9.1% (10.5% among girls and 7.6% among boys) (73). The prevalence rates calculated in this review were consistently higher than those reported in a similar review including studies published between 1990 and 2007 (7). The difference should, however, be interpreted with caution, as study designs and geographical region were too heterogeneous for the difference to be understood as an increase in MI prevalence over time. Secular trends in the prevalence of MI among children and adolescents have not been investigated to any large extent, and it is uncertain whether the prevalence is rising (73).

**Tension-type headache**

TTH is the most common, but least studied, form of recurrent headaches and little is understood about the biological nature of TTH in children and adolescents (84). Prevalence data on TTH are sparse and the variation of TTH prevalence is wide, ranging from 16% to 78% in different studies. The wide variation in prevalence rates might be due to different inclusion criteria, as TTH varies considerably in frequency, duration and intensity. The global prevalence of current TTH is estimated at 42% among adults and 31% among children and adolescents (70). A review of European studies reported a prevalence rate for TTH of 63% among adults and 16% in children and adolescents (69). The female-to-male ratio of TTH is 5:4, indicating that, unlike MI, women are affected only slightly more than men (42). The average age of onset is 25 to 30 years (85), the prevalence peaks between ages 30 to 39 and decreases slightly with age (86).

There are few follow-up or repeated prevalence studies on TTH, resulting in a gap in the knowledge of secular trends among both adults and adolescents. Some studies have shown an increase in the prevalence rates of TTH and non-migrainous headaches (15, 82, 87, 88), others have not (72).

**Gender and developmental factors**

The higher overall prevalence and severity of headaches, specifically MI and frequent headaches, among girls may be explained, in part, by developmental factors. During early childhood, recurrent headaches affect both genders equally (19, 89). In this period, the physiology, psychology and socio-cultural role expectations tend to be more similar
for girls and boys, than after the onset of puberty. Young children live mainly within the boundaries of the family, day care center and school, and are fully dependent on the social and physical resources that these structures provide. Adolescents have a broader access to the social and physical world beyond close relationships, and the differences in hormone-profile and physiology between females and males accelerates in puberty. In addition, gender-based differences in exposure to potential risk factors during adolescence, such as socio-cultural role expectations and limitations, lifestyle and psychosocial development (90-93) may increase girls’ susceptibility to recurrent headaches.

2.3 Comorbidity and risk factors

The term ‘comorbidity’, introduced by Feinstein(94), refers to the greater than coincidental association of two conditions in the same individual. There are several possible mechanisms of comorbidity: Symptoms of one condition may develop as a result of the other condition, shared environmental risk factors may underlie both conditions or genetic risk factors may produce a brain state resulting in both conditions (95). Children and adolescents with MI and recurrent headaches are more often diagnosed with other medical conditions. These include asthma, hay fever, anemia, epilepsy, being overweight, stomach or intestinal illnesses, psychiatric disorders, learning disabilities, sleep disorders and early menarche (17, 96). Most studies on comorbidity are done on MI among adults, adolescents and children, while the comorbidity of other headache forms is less far studied (17, 19). Comorbidity can significantly influence the delivery of medical care as it may confound diagnosis and provide special diagnostic challenges.

A risk factor is, according to WHO, any attribute, characteristic or exposure of an individual that increases the likelihood of developing a disease or injury (97). Since risk factors can often be modified, intervention to favorably alter them can reduce the probability of occurrence of disease. To evaluate risk factors for developing recurrent primary headaches, it is necessary to conduct longitudinal studies, preferably prospective, large-scale population-based studies.
The Young-HUNT studies, which include data on recurrent headaches, and numerous other diseases and complaints, provide a solid basis for studying headaches comorbidity. By repeating the study in the same population, it is also possible to detect probable risk factors for developing and maintaining recurrent headaches. In the present thesis, anxiety/depression, attention difficulties and conduct difficulties in relation to recurrent headaches were studied, in both a cross-sectional study (Paper II) and in a follow-up study (Paper III).

2.3.1 Psychiatric comorbidity in adolescence headaches

Clinical and population-based studies among adolescents have shown that headaches are associated with psychopathological symptoms, including both internalizing (mainly anxiety and depression) and externalizing problems (mainly behavioral problems). The association of recurrent headaches with anxiety and depression is consistent in most studies (98-104). Regarding behavioral problems, results from earlier studies are more divergent. Some studies among adolescents have found an association between recurrent headaches and attention difficulties and conduct difficulties (20, 98, 100, 102). However, other studies have been unable to confirm this association (105). It is still debated whether the headache might be considered the cause or the consequence of psychological symptoms (102). Results from longitudinal studies among adults suggest that the association between depression and MI may be bi-directional (106-109), possibly with shared genetic factors (110). Whether the psychological symptoms are more specifically related to MI than to TTH is unclear (20, 111). Similar to patients with other chronic pain conditions (112), adolescents with frequent and chronic daily headache have higher prevalence rates of psychopathological symptoms (113-115), indicating that headache frequency and severity, rather than type, increase the risk of comorbidity.

Symptoms of anxiety and depression – internalizing problems

Symptoms of anxiety and depression are, like recurrent headaches, subjective complaints without laboratory tests or other objective tests to confirm diagnoses. In studies with a broad scope there is often a need to collect information on mental health. However, clinical interviews are expensive and it may be problematic to include a long
list of questions on mental health in an already extensive questionnaire. In the Young-HUNT studies Symptom Check List 5 (SCL-5) was used to measure symptoms of anxiety and depression. The questions are described in detail later in this thesis (section 4.1 Materials and Methods). This short form checklist is based on statistical analyses of 23 of the items in the more extensive SCL-25 and has proven reliable in previous studies (116, 117). Neither SCL-25 nor SCL-5 are good instruments for differentiating between anxiety and depression, perhaps because the two kinds of symptoms are highly interrelated, in clinical as well as normal, populations. For most instances where a rather crude indicator of global mental health is sufficient, the SCL-5 is considered a safe screening instrument for symptoms of anxiety and depression (116, 117).

Behavioral problems (attention and conduct difficulties) – externalizing problems

The variability in estimates of psychopathology in the pediatric and adolescent headache population is likely caused by the differing diagnostic criteria used, for both the type of headache condition and the psychiatric symptoms. Some studies have used categorical assessment of psychiatric comorbidity defined by diagnostic criteria, while others have used dimensional measurements of psychological problems as discussed in section 6.3.

In the Young-HUNT questionnaire, adolescents were asked to consider 14 statements on school functioning. These statements were composed at the Norwegian Institute of Public Health and are included in earlier studies (118-120). Based on factor analyzes with eigenvalues, statements indicating attention difficulties and conduct difficulties were extracted (see section 4.1 Materials and Methods for details).
3 AIMS OF THE THESIS

The aim of this thesis was to study different aspects of recurrent headaches among adolescents.

The aims of the different papers were as follows:

- To look for changes in recurrent headache prevalence over a four-year period in two replicate population-based cross-sectional studies (Paper I).

- To analyze the prevalence of psychiatric comorbidity in relation to recurrent headaches and different types of recurrent headaches in a population-based cross-sectional study (Paper II).

- To investigate the relationship of symptoms of anxiety and depression and behavioral problems at baseline with recurrent headaches at follow-up four years later (Paper III).
4 SUMMARY OF RESULTS

4.1 Paper I

Earlier epidemiological studies have shown that recurrent primary headaches, such as MI and TTH, are frequent among adolescents. Very few replicate studies have re-evaluated the prevalence of primary headaches in this age group and it is uncertain whether it is increasing. The objective of the present paper was to compare the prevalence of primary headaches among adolescents aged 16 to 20 years in Norway in two periods. Two cross-sectional, population-based studies were conducted in Norway from 1995 to 1997 (Young-HUNT1) and from 1999 to 2001 (Young-HUNT2). In Young-HUNT1, 2594 adolescents in 2nd and 3rd grade of upper secondary school (aged 16 to 20 years) completed a comprehensive questionnaire including one question regarding headaches during the last 12 months. In addition, 1730 of the students were interviewed about their headache complaints. In Young-HUNT2, 2373 adolescents aged 16-20 years completed the same questionnaire and 1655 were interviewed in the same way as the earlier survey. The difference between headache prevalence in Young-HUNT1 and Young-HUNT2, and the difference of headache frequencies between the two studies, were analyzed with \( \chi^2 \) tests. Odds ratios (ORs) and 95\% confidence limits were calculated. The overall prevalence of having had headaches during the last 12 months did not change significantly (79.4\% versus 77.5\%; OR: 0.89, 95\%CI: 0.79-1.02, \( p=0.09 \)), whereas the prevalence of recurrent headaches increased from 30.3\% in Young-HUNT1 to 35.4\% in Young-HUNT2 (OR: 1.26, 95\%CI: 1.09-1.46, \( p=0.002 \)). The prevalence of TTH changed significantly, from 19.0\% to 21.9\% (OR: 1.20, 95\%CI: 1.02-1.42, \( p=0.03 \)). Also, the prevalence of MI tended to increase (7.5\% versus 8.7\%, OR: 1.18, 95\%CI: 0.92-1.52, \( p=0.18 \)). The overall frequency of recurrent headaches changed towards more monthly and less weekly headaches. In conclusion, our findings support the impression that the prevalence of recurrent headaches among adolescents is increasing, and underline the need for prospective designed studies with emphasis on prognosis and etiological factors.
4.2 Paper II

It is well documented that both anxiety and depression are associated with headaches, but there is limited knowledge regarding the relation between recurrent primary headaches and symptoms of anxiety and depression, as well as behavioral problems, among adolescents. Assessment of co-morbid disorders is important in order to improve the management of adolescents with recurrent headaches. The objective of the present paper was to assess the relationship of recurrent headaches with symptoms of anxiety and depression and behavioral problems in a large, population based, cross-sectional survey among adolescents in Norway. A total of 4872 adolescents aged 12 to 17 years were interviewed about their headache complaints and completed a comprehensive questionnaire that included assessment of symptoms of anxiety and depression and behavioral problems, i.e. conduct and attention difficulties. The participants were stratified in two age groups (12-14 years and 15-17 years) and the associations of recurrent headaches and headache frequencies with symptoms of anxiety and depression, as well as with behavioral problems, were estimated using logistic regression. Among adolescents aged 12-14 years, recurrent headache was associated with symptoms of anxiety and depression (OR: 2.05, 95%CI: 1.61-2.61, p<0.001), but not with behavioral problems. Among adolescents aged 15-17 years, there was a significant association between recurrent headaches and symptoms of anxiety and depression (OR: 1.64, 95%CI: 1.39-1.93, p<0.001) and attention difficulties (OR: 1.25, 95%CI: 1.09-1.44, p =0.001). Headache frequency was significantly associated with increasing symptoms scores for symptoms of anxiety and depression, as well as attention difficulties, evident in both age groups. The results indicate that both symptoms of anxiety and depression and behavioral problems are associated with recurrent headaches, and should, accordingly, be considered a part of the clinical assessment of children and adolescents with headaches. Identifying these associated factors and addressing them in interventions may improve headache management.
4.3 Paper III

The comorbidity of headaches and psychiatric symptoms is a well-recognized clinical phenomenon, but there are only limited data regarding the temporal relationship between headaches and symptoms of anxiety and depression, as well as behavioral problems in adolescents. The objective of the present paper was to investigate the relationship of symptoms of anxiety and depression and behavioral problems at baseline with recurrent headaches at follow-up four years later. Within the Nord-Trøndelag Health Study (HUNT), which include repeated population-based studies conducted in Norway, 2399 adolescents in junior high schools aged 12-16 years participated in Young-HUNT1 and in a follow-up study four years later, Young-HUNT2. The same comprehensive questionnaire that included assessment of symptoms of anxiety and depression and behavioral problems, i.e. conduct and attention difficulties was completed in both studies. In addition 1665 of the participants were interviewed about their headache complaints in Young-HUNT2. The associations of symptoms of anxiety and depression as well as behavioral problems at baseline with headache status at follow-up were assessed using binary logistic regression, estimating prevalence odds ratios (ORs) with 95% confidence intervals (CI). Higher scores of symptoms of anxiety and depression at baseline were associated with recurrent headaches at follow-up four years later (OR: 1.6, 95%CI: 1.2-2.1, p=0.001). This was evident for MI and NCH, but not statistically significant for TTH. Higher scores of symptoms of anxiety and depression at baseline were significantly associated with more frequent headaches at follow-up. Among adolescents without recurrent headaches at baseline, higher scores for symptoms of anxiety and depression were associated with new onset MI four years later (OR: 2.6, 95%CI: 1.1-4.8, p=0.036). Higher scores of attention problems at baseline were associated with NCH at follow-up (OR: 2.0, 95%CI: 1.3-3.4, p=0.017). In conclusion, results from the present study showed that symptoms of anxiety and depression in early adolescence were associated with recurrent headaches four years later. Clinicians should be aware of this relationship as it portends a poorer outcome for headache management and when these disorders are present together, their associated burdens and disabilities may be compounded.
5 MATERIALS AND METHODS

5.1 Study population
Nord-Trøndelag, one of 19 Norwegian counties, is located in the middle part of the country. The county has about 127,000 inhabitants, and consists of rural and industrial areas with few social differences. The population is scattered and no city has more than 21,000 inhabitants. The county is, however, a fairly representative cohort of the Norwegian population.

Young-HUNT1
During a two-year period, from August 1995 to June 1997, all students in lower secondary school (aged 12 to 16 years) and upper secondary school (aged 16 to 20 years) in Nord-Trøndelag County were invited to participate in the youth part of the Nord-Trøndelag Health Study, Young-HUNT. Junior high schools are obligatory in Norway, and although it is not compulsory, most adolescents attend high school as well. Individuals not registered in high school were identified by the ‘follow-up service’ of the County Education Authorities. In total, 8984 (88%) out of 10,202 invited individuals participated in the study (Figure 3). Most students who did not participate were absent from school on the day of the study, others did not get consent from their parents and some did not want to participate. The participating students completed a comprehensive self-administered questionnaire with more than 100 health-related questions, during one school hour. One of the questions was whether they had experienced any headaches during the last 12 months.

Headache diagnosis
Within a month of completing the questionnaire, a clinical examination including spirometry, weight, height and blood pressure measurements was performed in schools during school hours. The original intention was to interview the whole population about their headache complaints in connection with the clinical examination. Unfortunately, the interviews were not started until February 1996, which explains the lower number of interviewed individuals. During the ‘missed’ period, both rural and industrial areas were studied and there were no major differences in sex and age distribution between the total questionnaire-based study population and the questionnaire-based study.
population that was also interviewed. The total interviewed study population was 6174 (69%). Trained nurses performed the interviews, and the students were asked to report recurring headaches in the past 12 months that were not related to cold, fever or any other disease. Two typical headache symptom history descriptions, one for MI and one for TTH, were then presented (Table 2), and the students were asked to classify their headache according to the descriptions. A third alternative, NCH was given in case neither of the first two descriptions resembled their symptoms. Headache frequency during the past year was recorded according to the following categories: Less than 1 day per month (less than monthly), 1-3 days per month (monthly), 1-5 days per week (weekly), or more than 5 days per week (daily). The “recognition-based” headache diagnoses obtained by the nurses was validated against extensive semi-structured interviews by neurologists [14], and the agreement between the two methods was good (chance-corrected agreement (κ) 0.76). For MI, the positive and negative predictive values were 89% and 90%, respectively and for TTH 83% and 91%.

**Psychological symptoms**

Symptoms of anxiety and depression were measured by SCL-5, a five-item scale based on SCL-25, proven to be reliable in previous studies (116, 117). The items concerning symptoms of anxiety in the questionnaire were: Been constantly scared and uneasy, felt tense and restless, worried too much about different matters. The items concerning depressive symptoms were: felt hopeless when thinking of the future, felt down or sad. All questions had four alternative responses ranging from one: “not at all” to four: “extremely”. All five items were included in an anxiety/depressive variable as SCL-5 makes distinction between symptoms of anxiety and depression impossible. A mean score of the SCL-5 questions was computed, giving a scale ranging from one to four.

Variables concerning behavioral problems (attention and conduct difficulties) were derived from the school adjustment part of the questionnaire, including 14 items, described in previous studies (118, 119). The adolescents were asked: “Do any of these situations happen to you at school, or have they happened before?” with four alternative responses from one: “never” to four: “very often”. Attention difficulties were estimated by the question “How often do you have problems concentrating in class?” with an answer distribution from one to four. Conduct difficulties included how often the
participants “quarrel with the teacher”, “skip school”, “get into fights” and “get scolded by the teacher”. A mean score ranging from one to four was computed.

**Young-HUNT2**

In the school years 1999-00 and 2000-01, a follow-up study of Young-HUNT1 was performed. All students in 2nd and 3rd grade of upper secondary school (aged 16 to 20 years) in North-Trøndelag County and apprentices of the same age who participated in Young-HUNT1 were invited (n= 2969). It was a replicate study, with the same questionnaire, clinical examination and headache interview used in Young-HUNT1. In total, 2399 (81%) of the invited adolescents completed the questionnaire and 1665 (69.4%) were interviewed about their headache complaints (Figure 3).
Figure 3. The study population of Young-HUNT1 and Young-HUNT2
Table 2. Headache descriptions used in nurse interviews

**Alternative 1**
This headache often comes in attacks, the pain is moderate or severe, and may start on one side of the head. The headaches are pounding or pulsating, and I prefer not to move my head. I am often nauseated and may vomit. When I have this headache light or sounds bother me.

**Alternative 2**
This headache may start gradually and the pain is mild or moderate. The pain is usually located in the whole head, or in the neck. It feels like tightening or pressing (like a band around the head). I usually have no nausea or vomiting. When I have this headache I can normally carry on with my schoolwork, homework and normal physical activity.

**Alternative 3**
Neither alternative 1 or 2 describes my headache.
5.2 Statistical methods

Pearson’s chi-squared test ($\chi^2$)
When only categorical variables have been measured, frequencies have to be analyzed. The frequencies, or numbers, that fall into each combination of category can be tabulated in a contingency table. The simplest table has four different categories and is referred to as a 2 x 2 contingency table. $\chi^2$ test can determine whether there is a relationship between two categorical variables. This is an elegant statistical tool based on the idea of comparing the frequencies observed in certain categories to the expected frequencies in those categories by chance. The test has two important assumptions: Independence of data (each person contributes to only one cell of the contingency table) and the expected frequencies should be greater than 5 (121). $\chi^2$ test was used to analyze the difference in headache prevalence and headache frequencies between Young-HUNT1 and Young-HUNT2 (Paper I).

Binary logistic regression
Regression analysis is a way of predicting a continuous outcome variable from one continuous predictor variable (simple regression) or several continuous or categorical predictor variables (multiple regression) (122). Logistic regression is multiple regression but with an outcome variable that is a categorical variable and predictor variables that are continuous or categorical. It can be used to describe the relation between independent variables and a categorical outcome variable and at the same time control for the effect of other variables (123). In binary logistic regression the outcome variable has exactly two categories and this method was used to estimate the association of symptoms of anxiety and depression and behavioral problems with recurrent headaches (yes or no) in Papers II and III. The results were given with prevalence odds ratio (OR), corresponding confidence intervals (CIs) and $p$-values.
6 Methodological considerations

Epidemiologic headache studies pose a number of methodological problems, some of which are discussed in the following paragraphs. Accuracy in estimation is essential in epidemiologic studies and much attention is devoted to minimizing errors and assessing the impact of errors that cannot be eliminated. Sources of errors in estimation may be classified as either random or systematic (61, 124).

6.1 Random errors

Random error is when a value of the sample measurement diverges – due to chance alone – from that of the true population value (61). There are three major sources of random error: individual biological variation, sampling error and measurement error. Random error can never be completely eliminated since we can study only a sample of the population. Individual variation always occurs and no measurement is perfectly accurate. Sampling error is usually caused by the fact that a small sample is not representative of all the population’s variables and the best way to reduce sampling errors is to increase the size of the study. Measurement error can be reduced by stringent protocols and by making individual measurements as precise as possible. The opposite of random errors is precision and an estimate with few random errors may be described as precise (61, 125).

As previously mentioned, random error can be reduced by large sample sizes. It is also controlled by the use of statistical tests and p-value thresholds for significance that reduces the risk of misinterpreting random effects as real effects. In Papers I-III a p-value < 0.05 is taken to indicate statistical significance. This would signify that there is a less than 5% chance that an effect as strong as, or stronger than, the observed effect would occur by chance alone. Some caution is, however, required when interpreting significance levels. In classic epidemiological studies, several effects are often examined within the same study, without correcting for multiple testing (126). There is also a risk with health surveys such as HUNT, that a high number of possible associations are tested within the dataset by several research groups, and that only those yielding statistical significance are reported. If twenty hypotheses are tested, it is likely that one will give a significant result simply by chance. Having a clear idea of which hypothesis to
test, and what methods to use, prior to initiating the study can reduce this risk. Nevertheless, results from epidemiological research should be viewed as suggestive until replicated in independent cohorts or validated by experimental studies.

6.2 Systematic errors

Systematic errors in estimates are commonly referred to as biases, and occur when results differ in a systematic manner from the true value. Biases cannot be fixed statistically and have to be avoided from the start. The possible sources of systematic errors in epidemiology are many and varied; over 30 specific types of bias have been identified. The three main types are selection bias (nonresponse bias, exclusion bias, publicity bias), information bias (recall bias, reporting bias) and confounding.

The opposite of bias is validity, so an estimate that has little systematic error may be described as valid. The validity of a study is usually separated into two components: internal validity and external validity. Internal validity is the degree to which the results of an observation are correct for the particular group of people being studied. External validity, or generalizability, is the extent to which the results of a study apply to people outside that population (124). Internal validity is necessary for, but does not guarantee, external validity, and is easier to achieve. The external validity of a study is supported if similar results are found in studies in other populations (61) and the external validity of Papers I-III is discussed further in section 6.5.

6.2.1 Selection bias

Selection bias occurs when the subjects studied are not representative of the target population about which conclusions are to be drawn. There is a systematic difference between the characteristics of the people who participate in a study and the characteristics of those who do not (61). An obvious source of selection bias occurs when participants select themselves for a study, either because they are unwell or because they are particularly worried about an exposure (124). Selection bias can be a problem in clinic-based headache studies, as headache-sufferers referred to a clinic may have more severe headaches and more comorbidity than the general headache sufferer. In our study we have a large and unselected population, a relatively high participation
rate and no systematic selection of the interviewed participants, which indicates that the study cohort represents the population fairly well. There is probably little or no interest-related selection bias since headaches, and the other conditions investigated in our studies, were only a small portion of the subjects in Young-HUNT.

6.2.2 Information bias

If the individual measurements or classifications of disease or exposure are inaccurate (they do not correctly measure what they are supposed to), information bias occurs (61, 124). There are many sources of information bias and their effects are of varying importance. For discrete variables (variables with a countable number of possible values, such as indicator for sex), measurement error is usually called misclassification.

Differential misclassification

Differential misclassification occurs when the probability of being misclassified differs across groups of subjects (124). An example is recall bias, were subjects with the disease of interest tend to report previous exposure or symptoms differently from those without the disease. In the present study, most of the relevant questions were about recent symptoms and we do not think recall bias is a major problem. On the other hand, since both headaches, and a great number of the other variables, in the present study are self-reported, one cannot exclude the possibility of differential information bias related to different tendencies among the participants in reporting their symptoms (“reporting bias”). In studies on subjective complaints, the results may be influenced by a tendency to answer questions regarding different complaints in a similar way. Those who report their headache complaints might be more likely to report other complaints such as symptoms of anxiety and depression and behavioral problems (127). This may create strong associations that are explained by personality traits rather than biological mechanisms. However, the results in the present studies were in agreement with results from previous studies (20).

Nondifferential misclassification

Nondifferential misclassification is when all classes, groups, or categories of a variable (whether exposure, outcome or covariate) have the same probability of being
misclassified for all study subjects (124). In studies of comorbidity, valid definitions and reliable ascertainment of each of the disorders under consideration are essential (128). There are several limitations of the diagnostic precision in the Young-HUNT studies.

There is a possibility of nondifferential misclassification of headache subtypes that may weaken real associations. Modified versions of the IHS criteria for MI and TTH were used, and are further described, in sections 2 and 5. It can be difficult to distinguish between MI and TTH, especially in children and adolescents, and although we used a validated “recognition-based” headache diagnostic method in our study, nondifferential misclassification may have had an impact on the supplementary analyses (68). The headache groups in Young-HUNT, i.e. MI, TTH and NCH, were mutually exclusive. Other population-based studies have shown that TTH is very common among migraineurs (32, 82). Consequently, the prevalence of TTH may be underestimated. An advantage of our categorization of headaches was that so-called “double-counting” was avoided (127).

The use of questionnaires concerning symptoms of anxiety and depression is a well-validated method of assessing the true occurrence of such symptoms. The SCL-5 is considered a safe screening instrument for symptoms of anxiety and depression as discussed in section 2.3. The questions about school functioning used to define attention difficulties and conduct difficulties have not been validated, but have been used in earlier studies (118-120). Instead of dichotomizing into “high” and “low” problem scores, defining a high problem group as over the 70th percentile, we chose to use the psychological variables as continuous variables in the regression analyses. In this way the risk of nondifferential misclassification was reduced.

6.2.3 Confounding
The word “confounding” comes from the Latin confundere, meaning mix together. Confounding occurs when the observed result between exposure (risk factor) and disease differs from the truth because of the influence of a third variable (61). A confounding variable is a variable (measured or unmeasured) that is associated with both the disease and the exposure being studied. The variable must be a determinant of the occurrence of disease (i.e. a risk factor) and associated with the exposure under
investigation. Age, sex and social class are often confounders in epidemiologic studies (124). Confounding may lead to errors in the conclusion of a study, but, when confounding variables are known, the effect may be fixed (61, 123, 129). As Young-HUNT included so many variables it was possible to evaluate a broad spectrum of variables as possible confounders. In our studies we controlled for age, sex and family condition/single parenthood in the logistic regression analyzes (Paper II and III). However, one cannot rule out the possibility of residual confounding. Stress and childhood trauma (parental divorce, a lengthy hospital stay, prolonged parental unemployment, frequent parental drug or alcohol use) were found to have an impact on the relationship between major depression and MI in a population-based longitudinal study (130), and may be confounding factors in our studies.

6.3 Comorbidity assessment

One of the challenges in comparing research on psychiatric comorbidity in children and adolescents is the diversity of applied measurements. The majority of studies have applied dimensional measures of psychological and behavioral problems (131), but some clinical studies have used categorical assessments of psychiatric comorbidity defined by diagnostic criteria (Diagnostic and Statistical Manual of Mental Disorders (DSM) (132) or ICD (30)). The use of categorical assessments of psychiatric comorbidity defined by diagnostic criteria may appear to be the most valid choice of method. However, it is well recognized that psychiatric diagnoses in childhood and adolescence may fail to capture clinical levels of psychopathology, and dimensional measures have been recommended as they may improve accuracy (131, 133). Psychiatric diagnostics in children and adolescents often require information from multiple sources (the child/adolescent, parents and teachers) and expertise on childhood psychopathology. Reported dimensional measurements typically include a wide range of emotional and behavioral problems on a continuous scale, measuring frequency or intensity of symptoms, and indicating clinical levels for symptom scores. The Child Behavior Check List (CBCL) (134), measuring internalizing symptoms (depressive-, anxiety- and somatic problems) and externalizing symptoms (attention deficit/hyperactivity, oppositional and conduct problems) seem to be the most widely used instrument. Other examples are The Strength and Difficulties Questionnaire (SDQ) (135) and Hopkins Symptom Check
List (136). Epidemiological studies typically include shortened scales due to limited space, such as SCL-5 (116) used in Paper II and Paper III in this thesis.

6.4 Causality

In Paper II, we examined the relationship between headaches and psychiatric comorbidity using a cross-sectional analysis in Young-HUNT1. Although it is hard to prove causality in epidemiological studies, a classic set of criteria for causality was formulated for this purpose by Austin Bradford Hill in the 1960’s. His criteria are: temporal relationship, strength of association, dose-response effect, consistency, plausibility, specificity, coherence, experiment and analogy (137). In Paper II the relationship between recurrent headaches and symptoms of anxiety and depression was evident, and consistent with previously published findings in children, adolescents and adults. It also showed a dose-response relationship, in that more frequent headaches were associated with increasing symptoms scores for symptoms of anxiety and depression as well as attention difficulties. The strength of the relationship between recurrent headaches and behavioral problems was only moderate, and earlier studies have shown divergent results. However, the criterion of temporality (“exposure always precedes the outcome”) is considered the only absolute criterion, and can be examined only in a prospective design. To determine the direction of effect of the relationship between MI and psychiatric symptoms we used prospective data from Young-HUNT1 in Young-HUNT2. We selected a “population at risk” consisting of those who, at the time of Young-HUNT1, did not have recurrent headaches, and followed this group to Young-HUNT2. The study indicated that symptoms of anxiety and depression precede the onset of MI, strengthening the claim of a causal association. Nevertheless, causality cannot be definitely determined by cohort studies. It is possible that shared underlying factors, such as genetic risk variants, can lead to both disorders.

6.5 External validity

External validity, or generalizability, refers to the extent to which results from a study can be generalized outside of the study population (124). A prerequisite for external validity is internal validity, i.e. that the results hold true for the study population itself. Internal validity was discussed above, under the heading ‘systematic errors’. Evaluation
of external validity in epidemiological studies often focuses on the representativeness of the study sample. When studying a point estimate, such as the prevalence of a disease, this representativeness is often a critical issue for generalizability. However, when studying relationships between variables (such as those between MI/TTH and psychological risk factors), generalizability does not necessarily require that the study subjects themselves are similar to outside populations, only that the relations studied are (124). Reproducing results in other populations can directly test external validity and this is often required before the scientific community accepts new findings.

The Nord-Trøndelag County of Norway can be considered as fairly representative of Norway (138). The high participation rate in the questionnaire-based part of the study indicates that the study cohort represents the population fairly well, and that no serious selection bias was present. It also seems reasonable to assume that the prevalence rates of recurrent headaches based on data from the interviewed population are fairly representative. There was no systematic selection of subjects and no major differences in age and sex distribution between the total questionnaire-based study population and questionnaire-based study population that were also interviewed. It is possible that students absent from school, and, accordingly, not included in the study, might have more health problems than the responders, which, in turn, would lead to an underestimation of the observed prevalence rates of different headache disorders. This represents a possible limitation to the generalizability of our results. However, the prevalence of recurrent headaches in Young-HUNT1 (2) is comparable to that of European (69) and worldwide estimates (70), in which diagnoses were based on the same criteria (22, 25). The majority of participants in Young-HUNT2 had answered identical headache questions in Young-HUNT1. We cannot rule out the possibility that this resulted in the participants developing a familiarity with the HUNT surveys process, which may have had an impact on the way they responded to the questions. Validation of the results from Papers II and III in external populations should be sought. It would also strengthen the external validity if the biological mechanisms underlying the reported associations were identified by clinical studies.
7 Discussion

7.1 Headache prevalence

Reliable information of changes in prevalence of primary recurrent headaches over a period of time is important, both from a clinical, and a public health, perspective (82). Earlier follow-up studies examining changes in prevalence of recurrent headaches among children and adolescents have shown divergent results (8, 14-16, 87). The reasons for the discrepancy among different studies are not known, but they are probably due to differences in study methodology, diagnostic criteria, age groups and populations as well as geographical, sociocultural and ethnic factors. In addition, only a limited number of replicate studies of headache prevalence surveys among children and adolescents have been published.

In Paper I we found that the total prevalence of recurrent headaches among adolescents aged 16-20 years increased significantly over a four-year period. The overall prevalence of having had headaches during the last 12 months was relatively stable and tended to decrease. There was no significant change in MI prevalence, but there was a significant increase in the prevalence of TTH. Our findings support the impression that the prevalence of recurrent headaches among adolescents is increasing, but there was also a significant change towards more monthly and less weekly headaches. Changes in living conditions and habits, including increased stress and reduced physical activity, have been suggested as causal factors for the probable increase in the prevalence of recurrent headaches, but evidence is still lacking (6, 139).

7.2 Comorbidity and risk factors

Studying psychological correlates of headaches in the general population is important for many reasons. Firstly, depression is one of the leading causes of disability worldwide (140) and psychological symptoms in adolescents suffering from headaches may impact the outcome of conventional headache treatments. Adolescents with headaches and psychological problems use health services more than individuals without (141). Understanding and recognizing this comorbidity may, therefore, result in improvements in patient management (101). Secondly, current knowledge of the comorbidity of headaches is largely based on clinical samples with a high risk of selection bias and
limited generalizability to headache sufferers in general. Earlier epidemiological studies in children and adolescents have shown that headaches are associated with anxiety and depression, and also with attention and conduct difficulties (98, 100, 102). We still do not know the nature and direction of the relationship between recurrent headaches and comorbid psychiatric disorders, whether the relationship is related to attack frequency, or whether there exists an intrinsic and specific relationship between psychological factors and MI (142-144).

In Paper II we found that recurrent headaches were associated with higher levels of symptoms of anxiety and depression in adolescents aged 12-17 years. This association was evident for MI, TTH and NCH, supporting the view that this relationship is not specific to MI. Attention difficulties were associated with recurrent headaches, MI and NCH among those aged 15-17 years and conduct difficulties only with NCH in age group 15-17 years. There was no association between TTH and behavioral problems. Regarding behavioral problems and recurrent headaches results from earlier studies are divergent, probably mainly because of different diagnostic criteria both for headache diagnosis and behavioral problems. We did not use validated questions to measure attention and conduct difficulties, an important limitation of the study. Our study showed an association between recurrent headaches and behavioral problems, but not as consistent as that between headaches and anxiety and depression, and not evident for TTH.

Paper III showed that symptoms of anxiety and depression in early adolescence were associated with recurrent headaches four years later, evident for MI and NCH, but not for TTH. Symptoms of anxiety and depression were risk factors for developing MI, while attention problems increased the risk for developing NCH. These findings are consistent with earlier longitudinal studies, confirming that symptoms of anxiety and depression are associated with recurrent headaches, in particular MI.

**Mechanisms of comorbidity**

Clinical and population-based studies show that headaches is associated with psychopathological symptoms, including internalizing and externalizing problems, but whether these symptoms are specifically related to MI or TTH is not evident (102). In a
recent meta analyses, ten studies using the CBCL were selected, in order to assess internalizing (mainly anxiety and depression) and externalizing (mainly behavioral problems) symptoms in different types of headache versus healthy controls. Higher levels of internalizing symptoms were found in patients with either MI or TTH, while externalization symptoms were more pronounced among those with MI when compared to healthy controls. There was, however, no significant differences in psychopathological symptoms between the headache groups (20). This is in compliance with the results from Paper II, where internalizing symptoms were associated with MI and TTH when compared to headache free controls. Adversities in childhood, such as loss, injuries (145), or lack of social and economic resources within families, in schools and societies (146, 147) seem to be related to increased risk of headache complaints.

Shared risk factors may represent one pathway across somatic and psychological domains. In addition to environmental factors, shared genetic risk factors may also have an impact on the susceptibility to both headaches and psychopathological symptoms. With respect to headaches, heritability studies have mostly focused on MI and a meta-analysis of twin studies estimated the heritability of MI to be 45 % (148), indicating that genetic factors play a substantial role in this familial transmission. In recent years, new genetic risk variants have been identified for psychiatric disorders (149) and for common forms of MI (150), but so far little is known about the possible shared genetic risk factors for psychopathological co-morbidity in headaches though studies indicate that depression and MI may partly share underlying genetic risk factors (110, 151).

### 7.3 Implications

Psychological symptoms and headaches often co-exist. The conditions share common risk factors, and empirical data suggest that headaches may induce psychopathology and vice-versa. The fact that most studies are based on cross-sectional designs and cannot predict causality has drawn attention to longitudinal studies (20). Longitudinal studies have provided more solid evidence for bidirectional association between psychiatric disorders and headaches in adults (95, 107, 152). In children with frequent headaches there is an increased risk of developing psychiatric morbidity in adulthood (146). However, there is uncertainty in the literature regarding the direction of the
relationship between headaches and psychiatric symptoms among adolescents (102). Despite the uncertainties about the cause and direction of psychopathological symptoms in primary headache disorders, the clinicians confronted with young headache patients should take into account that comorbidity is, potentially, an additional detractor from their quality of life (153). In cases of adolescents with severe or refractory headaches and co-occurring psychological problems, their history may be the key to identifying potential factors contributing to onset, or maintenance, of complaints (154).

7.4 Ethical considerations

Health surveys, including HUNT, collect a range of sensitive personal and medical information about their participants. One major challenge is to maintain the confidentiality of participating individuals. The Data Inspectorate of Norway and the Regional Committee for Medical Research Ethics approved the HUNT study, and all information from HUNT was treated according to the guidelines of the Data Inspectorate. In our study, HUNT Research Centre identified all records, so that the study scientists did not know the identities of the participants. Nevertheless, due to the extensive information on each subject it is theoretically possible that a participant could be identified from these data alone. For all data files we followed a strict protocol to keep data within the research group. Participation in HUNT was based on a written informed consent from each participant in accordance with instructions from the Regional Ethics Committee. In addition, written consent from their parents was required for students below 16 years of age.
8 CONCLUSIONS AND FUTURE PERSPECTIVES

In this thesis we found that primary recurrent headaches are common among adolescents in Norway and that the prevalence increased over a four-year period. We found that recurrent headaches and, in particular, frequent headaches were associated with symptoms of anxiety and depression, and also with behavioral problems. It is important to consider the total burden of discomfort in adolescent headache sufferers in order to provide the best treatment. The prognosis and overall function may be determined not only by headache, but also by comorbid conditions. Early identification and management of risk factors among adolescents is important and may lead to better headache treatment and more effective strategies for preventing chronification of headaches. This underlines the need for prospective designed studies with emphasis on prognosis and etiological factors.
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