On the prevention of migraine

– focus on exercise and the patient's perspective

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To James, Noah and Nicole

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ABSTRACT

Migraine is a common neurological disorder causing huge suffering both for the individuals affected and for society. As migraine is a chronic disorder that cannot be cured, but merely relieved, prevention is of great importance. Exercise is often recommended in migraine prevention, but evidence of efficacy is still lacking. It can be difficult for patients with migraine to perform exercise, since heavy physical activity is a well-known trigger for migraine. It is known that pharmacological prevention is underused, but the patients' overall views and experiences of migraine prevention have not been sufficiently studied.

The overall aim of this thesis was to evaluate different aspects of physical activity in relation to headache, especially the possible preventive effects of exercise in migraine. Furthermore, it aimed to elucidate the complexity of migraine prevention from patients' perspectives. Study I was divided into a prospective and a cross-sectional part aiming to evaluate the relationship between level of physical activity and migraine and non-migraine headache. This was done using data from the Nord-Trøndelag Health Surveys. Study II was an intervention study aiming to evaluate a method of exercise, for untrained patients with migraine, regarding improvement of exercise capacity and migraine status. Study III was a randomized controlled study in which exercise was compared with common pharmacological and non-pharmacological treatments with regard to migraine prevention. Study IV was a qualitative study using content analysis to elucidate migraine prevention from a patient perspective.

The main findings were that individuals with migraine and other types of headache are less physically active than headache-free individuals. There was also a strong linear trend of higher prevalence of 'low physical activity' with increasing headache frequency. It can be difficult for patients with migraine to perform exercise. An exercise programme based on aerobic exercise led by

a physiotherapist showed no deterioration in migraine status: to the contrary, migraine status improved, and so did maximal oxygen uptake (VO_{2max}) and quality of life. The effect of exercise in the randomized controlled study did not significantly differ when the reduction in migraine frequency was compared with common and well-documented pharmacological and non-pharmacological options. Increased VO_{2max} was significantly improved in the exercise group compared with the other two treatments, and side effects were only seen in the pharmacological group. The findings suggest that exercise may be an option for the prophylactic treatment of migraine in patients who do not benefit from, or do not want, daily medication. The patients' views on prevention are also important to consider in migraine prevention. A balance between letting it influence life completely and not letting it influence life at all is described, and in both directions there is a risk that life is very much controlled by migraine. Accepting the disease and the fact that migraine prevention must influence life to some degree is suggested as a way of taking control. Further, an appraisal of the advantages and disadvantages of different treatments, attitudes, support, and knowledge influences the choice of prevention strategies.

In conclusion, people with headache, including migraine, are less physically active than people without headache. For patients with migraine, maximal oxygen uptake can increase without deterioration of migraine status through physiotherapist-led exercise three times a week. Exercise is suggested as a means of migraine management, but the strategies patients choose to use depend upon individual preferences. Decisions regarding prevention are also affected by the patients' perspectives of their illness.

Keywords: headache, physical activity, exercise, chronic disease, rehabilitation, physical therapy, relaxation, prevention, quality of life, attitudes, knowledge, experiences

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SAMMANFATTNING PÅ SVENSKA

Migrän är en vanlig neurologisk sjukdom som orsakar stort lidande både för den drabbade patienten och samhället. Eftersom migrän är en kronisk sjukdom, som inte kan botas utan endast lindras, är prevention av största vikt. Fysisk träning rekommenderas ofta i förebyggande syfte, men ännu finns inga bevis för dess effekt. Det kan vara svårt för personer med migrän att utöva fysisk träning, då hård fysisk aktivitet är en välkänd triggande faktor för migränanfall. Studier har visat att farmakologisk profylax är underutnyttjad, men när det gäller patienternas uppfattning i största allmänhet kring att förebygga migrän, finns endast begränsad kunskap.

Det övergripande syftet med avhandlingen var att utvärdera olika aspekter av fysisk aktivitet och huvudvärk och att undersöka möjliga förebyggande effekter av fysisk träning vid migrän. Ett ytterligare syfte var att beskriva komplexiteten i att förebygga migrän utifrån ett patientperspektiv. Studie I består av; en prospektiv studie och en tvärsnittstudie med syftet att utvärdera eventuella samband mellan nivå av fysisk aktivitet och huvudvärk. Detta gjordes med hjälp av data från Hälsoundersökningen i Nord-Trøndelag (HUNT). Studie II syftade till att utvärdera en träningsmetod för otränade personer med migrän avseende syreupptagningsförmåga och migränstatus. Studie III var en randomiserad kontrollerad undersökning där fysisk träning som förebyggande migränbehandling jämfördes med välutvärderade effektiva farmakologiska och icke-farmakologiska metoder. Studie IV var en kvalitativ studie där kvalitativ innehållsanalys användes för att beskriva migränprevention ur ett patientperspektiv.

De huvudskaliga fynden i avhandlingen är att individer med migrän och annan huvudvärk är mindre fysiskt aktiva än individer utan huvudvärk. Ett samband mellan högre frekvens av huvudvärk och låg fysisk aktivitetsnivå sågs också. Det kan vara svårt för människor med migrän att träna fysiskt, men genom ett träningsprogram handlett av sjukgymnast, tre gånger i veckan, kunde otränade personer med migrän öka sin maximala syreupptagningsförmåga utan att migränstatus förvärrades. Snarare visade sig fysisk träning ha en positiv effekt på antalet migränanfall, och förbättringen var likvärdig med effekten av avslappningsträning eller läkemedlet Topimax®. Fysisk träning kan därför övervägas som förebyggande behandling av migrän, framför allt hos patienter som inte vill eller inte kan ta förebyggande mediciner. Träningen resulterade också i ökad maximal syreupptagningsförmåga, till skillnad från de andra behandlingarna.

Vidare är patienternas syn på att förebygga sin migrän också viktigt att ta hänsyn till vid valet av behandling, där patientens perspektiv på sin sjukdom spelar en roll. En balans beskrivs mellan att låta migränprevention påverka hela livet och att inte låta det påverka livet alls, vilket i båda riktningar kan leda till ett liv i hög utsträckning kontrollerat av migränsjukdomen. Genom ökad kunskap och stöd kan patienterna få hjälp att hitta metoder för att förebygga migrän, vars eventuella negativa aspekter de kan acceptera för att få del av de positiva effekterna. Detta kan ses som ett sätt att ta kontroll över sin sjukdom.

En slutsats av avhandlingen är att förekomsten av huvudvärk i befolkningen är associerad till graden av fysisk aktivitet. Individer med migrän, som tränade under handledning av sjukgymnast, fick en ökad syreupptagningsförmåga och färre migränanfall. Fysisk träning kan således vara ett alternativ till migränförebyggande behandling, men valet av förebyggande strategier är individuellt utifrån den enskilde patientens preferenser. Hur patienten ser på sin sjukdom är också av betydelse för effektiv migränprevention.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals. The papers are printed with kind permission from the publishers.

I. Varkey E, Hagen K, Zwart JA, Linde M. Physical activity and headache: results from the Nord-Trøndelag Health Study. Cephalalgia 2008;28:1292–7.

II. Varkey E, Cider Å, Carlsson J, Linde M. A study to evaluate the feasibility of an aerobic exercise program in patients with migraine. Headache 2009;49:563–70.

III. Varkey E, Cider Å, Carlsson J, Linde M. Exercise as migraine prophylaxis: a randomized study using relaxation and topiramate as controls. Cephalalgia 2011;31:1428–38.

IV. Varkey E, Linde M, Henoch I. 'It's a balance between letting it influence life completely and not letting it influence life at all': a qualitative study of migraine prevention from the patients' perspectives. Submitted.

CONTENTS

ABBREVIATIONS

ACSM	American College of Sports Medicine
AE	Adverse events
CDH	Chronic daily headache
CGRP	Calcitonin gene-related peptide
CI	Confidence interval
CNS	Central nervous system
HRQoL	Health-related quality of life
ICHD-II	International Classification of Headache Disorders, 2nd ed.
IHS	International Headache Society
IPAQ	International Physical Activity Questionnaire
ITT	Intention to treat
MSQoL	Migraine-Specific Quality of Life
OR	Odds ratio
PP	Per protocol
RCT	Randomized controlled trial
RPE	Rate of perceived exertion
SF-36	Short form 36
TTH	Tension-type headache
VAS	Visual analogue scale
5-HT	Serotonin

DEFINITIONS IN BRIEF

Cohort study	A study comprising people having something in common when the group is first assembled. The group is followed over time to observe the development of outcome events. Individuals within cohorts may be healthy at first, and then followed for the emergence of specific diseases (1).
C*onfounding*	Something that occurs when factors are associated and the effect(s) of one is confused with or distorted by the effect of others (2).
Cross-Sectional study	A study of a stratified group of subjects at a specific point in time. Conclusions are drawn about a population by comparing the characteristics of those individuals (1).
Odds Ratio	Odds ratio (OR) can be used when studying the likelihood of an individual belonging to a certain outcome or group, when a specific characteristic is given and when it is compared with someone in a reference group who does not have this specific characteristic. OR > 1 means that the individual with the presence of the specific characteristics is more likely to belong to the given group. Conversely, OR < 1 means that individuals in the reference group without the specific characteristics are more likely to belong to the group of interest. OR = 1 means that individuals with or without the given characteristics are equally likely to belong to the group (1).
Physical activity	Any bodily movement, produced by skeletal muscles that result in energy expenditure (3).

Exercise	A subset of physical activity that is planned, structured, repetitive, and purposeful in the sense that improvement or maintenance of physical fitness is the objective (3).
Reliability	The extent to which repeated measurements of a stable phenomenon by different people and instruments at different times and places yield similar results (2).
Selection bias	Occurs when comparisons are made between groups of patients that differ in determinants of outcome other than what is under study (2).
Validity	The degrees to which the data measure what they were intended to measure—that is, the results of a measurement corresponds to the true state of the phenomenon being measured (2).
Qualitative content analysis	A research method for making replicable and valid inferences from data to their context, with the purpose of providing knowledge, new insights, a representation of facts, and a practical guide to action (4).

PREFACE

I was a four-year-old girl the first time I came across migraine. I can still remember the smell of my mum's perfume—which I normally loved—but sometimes just felt way too strong. Connected with this, I had intense pain just behind one of my eyes and also felt very sick. This 'eye-disease' happened to me many times over the years, and it was actually not until 16 years later that I realized that all the symptoms together made up a common neurological disorder affecting the lives of millions of people all over the world.

When I started to work as a physiotherapist, I worked at a specialist clinic for headache, Cephalea Headache Centre. I was given a unique opportunity to combine clinical work with research. This was where my dream about a thesis started, and the aim of it grew during the years of clinical work. First, I wanted to evaluate non-pharmacological options in migraine prevention, which the patients requested. Exercise, which always has been an important part of my life, also became my research subject. Starting a randomized controlled study, I realized that evidence was not everything. The patients actually have to use the evidence-based methods to be able to achieve positive effects. That was why I wanted to complement my research with a qualitative study from the perspective of the patients. How do patients reason regarding preventing their disease? What experiences do they have concerning prevention? I wanted to know more.

My life has been enriched by my research. Now my wish is that this work can benefit people in health care working with migraine prevention, and especially the patients who are suffering from and struggling with this sometimes horrible disease.

INTRODUCTION

This dissertation deals with migraine and migraine prevention from an external and an internal perspective, that is the perspective of health care and the perspective of the patients who are suffering from the disease. Further, migraine prevention is seen from the view of a physiotherapist. Migraine is a common neurological disorder causing huge suffering, both for the individuals affected and for society, and as migraine is a chronic disorder which cannot be cured, but merely relieved, prevention is of great importance.

Migraine

Clinical manifestations of migraine

Migraine is a chronic neurological disorder causing attacks of severe headache and nausea, and an increased reactivity to sensory stimuli. A low migraine threshold is caused by genetic factors (5). Migraine is not one, but a group of syndromes, where the most common subtype is *migraine without aura*. Migraine without aura generally manifests as attacks that last between 4 and 72 hours. Typical characteristics of these attacks are unilateral headache with pulsating quality; moderate or severe intensity; aggravation by routine physical activity; and associated nausea, photophobia, and phonophobia. Some patients experience a premonitory phase (prodrome), which occurs hours to days before the headache starts, and a headache resolution phase after the release of the headache. The premonitory and the resolution phases can involve symptoms such as hyperreactivity, hypoactivity, depression, craving for particular foods, and repetitive yawning. Migraine with aura is another common type of migraine. It differs from migraine without aura in that it also includes attacks of reversible focal neurological symptoms before the headache phase starts. These symptoms usually develop gradually over 5–20 minutes and last for 60 minutes. It is not uncommon that patients have migraine both with and without aura (6).

Pathophysiology and triggering factors

Migraine attacks may be induced by one or several triggering factors, the most common of which are stress, hormone fluctuations in women, not eating, weather changes, sleep disturbance, perfume or odour, neck pain, light, alcohol, smoke, sleeping late, heat, certain types of food, exercise, and sexual activity (7), as described in Figure 1. The migraine disorder is

suggested to be caused by a neuronal hyper excitability, secondary to an altered mitochondrial energy metabolism, a dysfunction in ion transport over cell membranes in the central nervous system (CNS), low levels of magnesium in brain tissue, and altered levels of signal substances such as 5-HT (serotonin) (8-10). During the pain phase of migraine, potent, vasoactive neuropeptides, such as calcitonin gene-related peptide (CGRP), are released from the trigeminal nerve fibres, which possibly results in a sterile inflammation and dilatation of vessels. This trigeminovascular inflammation may be a self-perpetuating vicious circle, with uni- or bilateral painful perception (11). It has also been hypothesized that the release of endogenous nitric oxide (NO) from blood vessels, perivascular nerve endings, or brain tissue triggers the pain. Further, suddenly changing systemic 5-HT levels have been associated with migraine headache (12) and the autonomic nervous system might play a role, as well (13). Migraine is, in summary, considered to be a primary disorder of the CNS with secondary vascular effects, a neurovascular disorder (5).

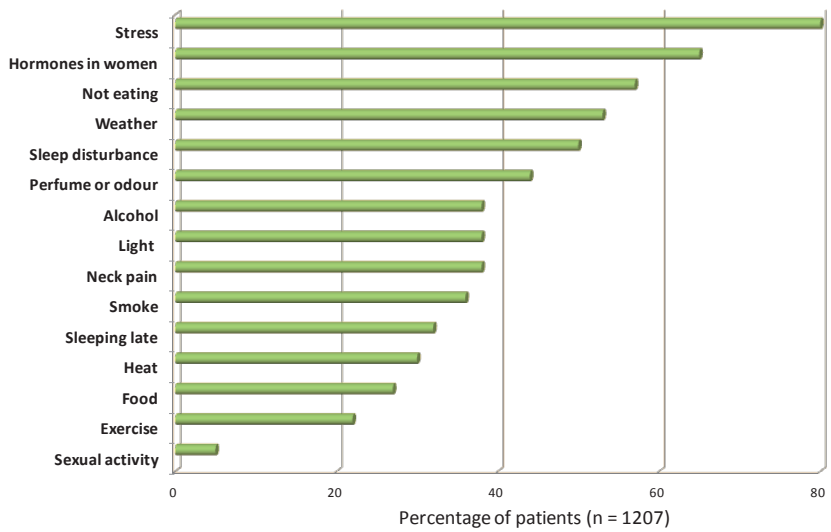


Figure 1 Common triggering factors for migraine, adapted from Kelman (7).

Diagnosis

A headache diagnosis is based mainly on anamnestic data, but preferably also on physical examination, and in some cases, a normal laboratory investigation to rule out secondary headaches (5). The International Headache Society (IHS) has developed a system of headache classification, the International Classification of Headache Disorders, 2nd ed. (ICHD-II) (6), which is the most important guideline used for diagnosis and management of headache. In Table 1 the diagnostic criteria for migraine are described.

Societal burden

Migraine includes a huge functional limitation and also a great economic burden (14–15). The burden of migraine on society has been described by the World Health Organization, which includes severe migraine in the highest disability class, emphasizing that this illness represents a serious health problem both for individuals and for society (16). The one-year prevalence in Sweden is approximately 13% (17), and globally, most epidemiological studies show similar incidence and prevalence (18). The prevalence is higher in women (12–25%), than in men (5–9%) (19), and symptoms are also more severe among women than men (17). The higher incidence, severity, and frequency in women may be explained by genetic factors and fluctuations in hormones (18).

Burden for the individual bearer

Migraine is not only a public health problem. It is mainly a huge burden from an individual perspective. It may significantly impact occupational or academic performance, social activities, and family life (20–21). Patients with migraine are not only affected during attacks; they can also be affected between the attacks (14, 20). Migraine bearers are shown to have reduced health-related quality of life (HRQoL) not only compared with control subjects (22), but also compared with patients with other chronic diseases. Using the Short Form 36 (SF-36) questionnaire, HRQoL in migraine was compared to other conditions (diabetes, hypertension, depression, and osteoarthritis). Results from that study showed that the patients with migraine experienced significantly more pain and restrictions to their daily activities than patients from the other disease groups (23). Several epidemiological studies have shown that migraine often is present in conjunction with a number of psychiatric disorders, including generalized anxiety disorder, major depressive disorder, panic disorder, bipolar disorder, and personality disorders (24–30). Migraine with aura may also in rare cases lead to ischemic damage of the brain (31).

Table 1 Diagnostic criteria for migraine with and without aura (6).

Diagnostic criteria for migraine without aura (IHS 1.1)
A. At least 5 attacks fulfilling criteria B–D
B. Headache attacks lasting 4–72 hours (untreated or unsuccessfully treated)
C. Headache having at least two of the following characteristics:
1. Unilateral location
2. Pulsating quality
3. Moderate or severe pain intensity
4. Aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)
D. During headache, at least one of the following:
1. Nausea and/or vomiting
2. Photophobia and phonophobia
E. Not attributed to another disorder
Diagnostic criteria for migraine with aura (IHS 1.2)
A. At least 2 attacks fulfilling criterion B
B. Migraine aura fulfilling criteria B and C for one of the subforms 1.2.1–1.2.6
C. Not attributed to another disorder
1.2.1 Typical aura with migraine headache
A. At least 2 attacks fulfilling criteria B–D
B. Aura consisting of at least one of the following, but no motor weakness:
1. Fully reversible visual symptoms including positive features (e.g. flickering lights, spots, or lines) and/or negative features (i.e. loss of vision)
2. Fully reversible sensory symptoms including positive features (i.e. pins and needles) and/or negative features (i.e. numbness)
3. Fully reversible dysphasic speech disturbance
C. At least two of the following:
1. Homonymous visual symptoms and/or unilateral sensory symptoms
2. At least one aura symptom developing gradually over ≥5 minutes and/or different aura symptoms occuring in succession over ≥5 minutes
3. Each symptom lasts ≥5 and ≤60 minutes
D. Headache fulfilling criteria B–D for 1.1 Migraine without aura beginning during the aura or following aura within 60 minutes
E. Not attributed to another disorder

Living with a chronic illness

In a qualitative study of experiences and perceptions of people with headache, patients report that the headaches make it difficult to carry out daily activities. A negative impact on mood is also described, which includes feeling depressed or down, self-pity, embarrassment, and aggression. On the other hand, patients reported the importance of getting on with things and not letting the headache govern them (32).

There are many theories describing life with a chronic illness. The Shifting Perspectives Model of Chronic Illness arose from a synthesis of qualitative research findings on experiences of living with diseases such as diabetes, spinal cord injury, and rheumatoid arthritis (33). The findings may be transferred also to living with frequent migraine. This model shows that living with a chronic illness is an ongoing, continually shifting process, in which people experience a complex dialectic between themselves and their world. The perspective of chronic illness contains elements of both illness and wellness, which are described in two shifting perspectives, *illness in the foreground* and *wellness in the foreground* (Figure 2).

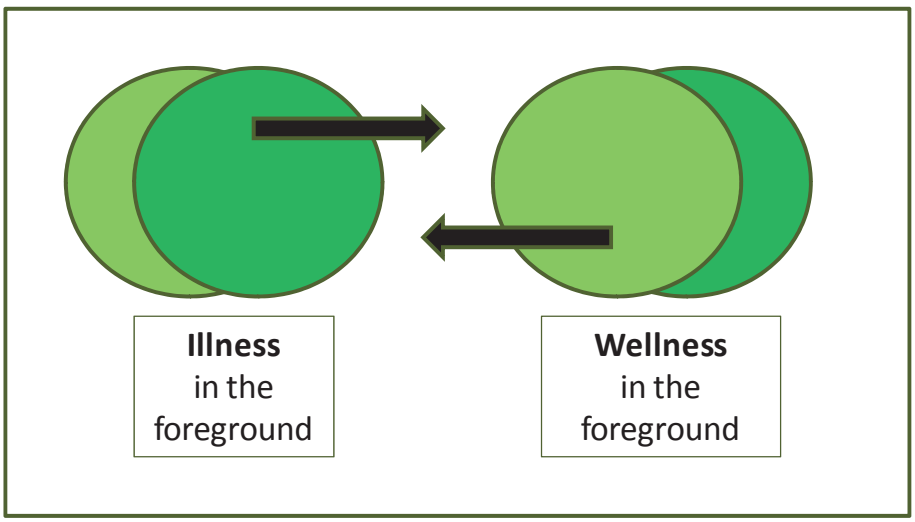


Figure 2 The Shifting Perspectives Model of Chronic Illness adapted from Paterson (33).

The experience of illness, as well as its personal and societal context, influences the degree to which illness is in the foreground or in the background. The perception of reality is the essence of how people with chronic illness interpret and respond to their illness.

The illness in the foreground perspective is characterized by a focus on the sickness, suffering, loss, and burden associated with living with chronic illness. This makes the illness destructive to oneself and to others. The opposite perspective, wellness in the foreground, includes an appraisal of the chronic illness as an opportunity for meaningful changes in relationships with the environment and others. Within this perspective, the self, not the diseased body, becomes the source of identity. The body is not what controls the person. This perspective can be gained by increased knowledge about the disease, support in the environment, and identifying how one's body responds. This perspective includes a distance from the sickness, which allows a focus on the emotional, spiritual, and social aspects of life, rather than primarily on the diseased body. A major factor influencing a shift from wellness to illness in the foreground is the perception of a threat to control that exceeds the person's threshold of tolerance.

A multidisciplinary approach to migraine management

To reduce the frequency and burden of primary headache, as well as the risk for medication-overuse headache, a multidisciplinary headache treatment is suggested (34). Multidisciplinary approaches are gaining acceptance also in migraine management. It is not clear, though, which elements are relevant in such a team and which combinations of treatment strategies should be applied. Suggestions are to include neurologists, behavioural and clinical psychologists, physiotherapists, and headache nurses, supplemented by consultants from psychosomatic medicine, psychiatry, and dentistry, if needed.

The role of a physiotherapist in migraine rehabilitation

A central concept in physiotherapy is human movement (35). According to the World Confederation for Physical Therapy, physiotherapy includes developing, maintaining, and restoring maximum movement and functional ability throughout the lifespan, which comprise different circumstances where movement and function are threatened by ageing, injury, diseases, disorders, conditions, or environmental factors (36). Functional movement is also central to the meaning of being healthy. Physiotherapy is therefore concerned with identifying and maximizing quality of life and movement potential, which encompasses physical, psychological, emotional, and social wellbeing.

The physiotherapist has traditionally not had a central role in migraine prevention. On the contrary, the role of physiotherapy is questioned and the effects of treatment are not enough studied (37). It is more common that the physiotherapist has a role in the treatment of patients with secondary headaches, especially those related to a disorder of the musculoskeletal system. Physiotherapy will then include an examination of the musculoskeletal system and an evaluation as to whether it contributes to the patient's headache symptoms (38).

The term 'physiotherapy' in migraine treatment refers in the literature to techniques and methods like exercise or manual techniques, that is postural corrections, soft tissue work, stretching, active and passive mobilization, and manipulation techniques (39). However, physiotherapy involves a wide range of treatment modalities, which can be relevant in migraine treatment (40). Examples of such treatments are acupuncture, stress management techniques, relaxation therapy, biofeedback, massage, and transcutaneous electric nerve stimulation (TENS) (41–42). Physiotherapy is also concerned with counselling and educating patients about pain, self-care, ergonomics, and so on (40).

Prophylactic treatment of migraine

In the management of migraine, acute treatment can be supplemented by pharmacological and non-pharmacological prophylaxis. There is no commonly accepted indication for when to start prophylactic treatment. According to European Federation of Neurological Societies Task Force guidelines, prophylactic drug treatment should be considered and discussed with the patient when important life domains are severely impaired, the frequency of attacks is two or more per month, acute treatment fails, or when auras are very disturbing (43). Below, a brief overview of both pharmacological and non-pharmacological treatments will be given with emphasis on topiramate, behavioural therapy including relaxation, and exercise, which are studied in this thesis.

Prophylactic drugs

The drugs of first choice are beta blockers (metoprolol and propanolol), calcium channel blockers (flunarizine), and antiepileptic drugs (valproic acid and topiramate) (Table 2). Drugs of second choice include amitriptyline, naproxen, petasites, and bisoprolol. When choosing a prophylactic drug, the potential side effects should be considered (43).

Table 2 Recommended drugs of first choice, Grade A, for the prophylactic drug treatment of migraine (43).

Substance:	Daily dose in mg:
Betablockers	
Metoprolol	50–200
Propanolol	40–240
Calcium channel blockers	
Flunarizine	5–10
Antiepileptic drugs	
Valproic acid	500–1800
Topiramate	25–100

Topiramate in migraine prophylaxis

Topiramate is one of the drugs of first choice in the pharmacological prophylaxis of migraine (44). Several large, randomized, placebo-controlled trials have proven topiramate to be effective for migraine prevention in adults (45–47) with 100 mg/day being the target dose. Efficacy variables used in the studies were reduction in migraine frequency, use of acute medication, and improvement of quality of life evaluated by the Migraine Specific Questionnaire (MSQ) and the SF-36. The benefits are shown to appear after the first month of treatment and persist throughout the subsequent 6-month treatment period. Data from two studies show that the benefits were sustained with prolonged treatment up to 12–14 months (48–49).

The efficacy of topiramate in migraine seems to be mediated by the interaction with several sites of action. The drug decreases the frequency of action potentials elicited by depolarizing electric current, giving expression to a blockade of voltage-dependent Na+ channels. Topiramate modulates cortical excitability in patients with migraine. This effect alone does not seem to explain the drug's efficacy in migraine prophylaxis, though. Topiramate inhibits the excitatory activity of glutamate. It also inhibits neurons of the trigeminocervical complex. Furthermore, topiramate inhibits the release of CGRP from prejunctional trigeminal neurons. An inhibitory effect on high-voltage-dependent Ca2+ channels, especially in the periaqueductal grey region, is a possible mechanism to explain the therapeutic effect in migraine. A reduction in excitatory transmission and an increase in inhibitory neurotransmission are suggested (50).

Non-pharmacological treatments

There are a range of non-pharmacological treatments for migraine. To educate patients about headache and management strategies, identifying triggering factors for migraine and modifying the lifestyle are important actions in migraine prevention (51). In addition, specific non-pharmacological interventions can be used either alone or in conjunction with ongoing pharmacological interventions. Drugs and non-pharmacological methods have in some studies shown equal effect (52–53). Behavioural therapies, including relaxation training, biofeedback, and stress management, are evidence-based methods (53). Beside behavioural therapies, recent positive findings from randomized trials in acupuncture also show consistent evidence in migraine treatment (41). As of today, other complementary and alternative techniques are not sufficiently evaluated to be recommended in migraine prevention, but they may be used if the patient prefers this approach or when other more evaluated interventions (non-pharmacological or pharmacological) have not provided adequate results (51). These can include, for example, manual therapies, exercise, and TENS (39, 54–55).

Avoidance of triggering factors and lifestyle changes

To find and avoid triggering factors for migraine is an important and a common recommendation in migraine treatment. By definition, exposure to a triggering factor increases the probability of headache onset for a clinically relevant time period, usually minutes to days (51). The purpose of finding these triggering factors is primarily to avoid them, and thereby reduce attack frequency. Some triggering factors are beyond the patient's control, such as hormone fluctuations and changes in weather, and for some patients it is hard to find their specific triggering factors. Furthermore is the evidence of the impact of managing triggers on headache primarily anecdotal (51) and it can sometimes be stressful trying to avoid all of them.

Exposure to triggering factors like disturbing sounds, light, and stress have been studied for shorter and longer periods of time. It is shown that shorter exposure to the factor could increase sensitivity to it, and a longer exposure could reduce the sensitivity (56–60). To avoid all triggering factors could therefore potentially lead to increased sensitivity and more headache attacks in the long run (60). Good advice could therefore be to identify triggering factors and use either avoidance or management strategies to improve headache control (51, 56, 61). Besides avoidance of triggering factors, lifestyle changes are often recommended. These usually include regular sleep and meals, exercise and, stress reduction (51).

Behavioural therapies

Different behavioural therapies are well studied and often used in migraine prevention. The term includes relaxation, biofeedback, and cognitive behavioural therapy or stress management (62). Behavioural therapies provide the patient with tools to manage their physiological and psychological responses to stressors that are an inevitable part of life (51). Patients are taught relaxation techniques to minimize physiological responses to stress and decrease sympathetic arousal. Relaxation therapy can include progressive muscle relaxation (63), autogenic relaxation training (64), and meditation or passive relaxation (65). The type of training does not seem important in headache improvement (66). According to the United States Headache Consortium, grade A evidence is given to relaxation training, a combination of thermal biofeedback and relaxation training, electro-myography biofeedback, and cognitive behavioural therapy in migraine prevention (67).

Acupuncture

A Cochrane review (41) evaluating acupuncture in migraine prophylaxis was published in 2009. It concluded that there is consistent evidence that acupuncture provides additional benefit to treatment of acute migraine attacks only or to routine care. Acupuncture is shown to be at least as effective as, or possibly more effective than, prophylactic drug treatment, and has fewer adverse effects. For this reason, acupuncture should be considered a treatment option for patients willing to undergo this treatment.

In conclusion, behavioural therapies and acupuncture are evidence based, but still, many non-pharmacological options are not sufficiently studied, and therefore, at present, lack evidence (Table 3).

Table 3 Evidence-based non-pharmacological options in migraine prevention.

Intervention type:	Evidence grade:
Behavioural interventions:	
Relaxation training	A[67]
EMG biofeedback	A[67]
Thermal biofeedback	A[67]
Cognitive-behavioural therapy	A[67]
Acupuncture	Consistent evidence[41]

EMG = electromyography

Barriers to migraine prophylaxis

An important barrier in the treatment of migraine is that many patients do not consult a physician. A Swedish epidemiological study (20) showed that 44 % had never seen a physician for their migraine and similar results are seen in other studies (68–71). It is further known that among patients with two or more migraine attacks per month, most do not use prophylactic medication, even if they might want to (72). Among the users only a few are taking preventive medications continuously (73). This leads to another important barrier to effective migraine treatment; despite the existence of scientific evidence and their recommendations in guidelines, preventive medications are still underused in clinical practice, and many patients are thus not receiving the likely benefits available (74–79).

After overcoming the barriers of not consulting a physician and not using preventive medications, it is essential that the patient adhere to the actual treatment. Since migraine is a chronic disorder with episodic attacks or daily headache, preventive treatment must be maintained for a long time, and adherence to treatment can therefore be difficult. Four important determinants of medication adherence are described (80): Disease driven (the disease must be seen as important for the patients to be motivated); medication driven (good tolerability may be associated with high adherence); physician driven (engaging the patients in treatment by providing information, knowing the patients' expectations, etc.) and patient driven (factors associated with the decision-making process about using medications). A few publications examine adherence to prophylactic migraine drug treatment. They show that 25–50% of patients are non-adherent to medications (81–84). However, when factors associated with adherence were studied, neither attack frequency, duration of attacks, degree of recovery between attacks, nor cardinal symptoms during attacks were significantly associated with adherence (84). One study showed that involvement in the decision making to choose preventive medication was the most important factor for adherence to migraine prevention (85), and in another study efficacy was rated as highest (78). Other factors mentioned were that the physician took time to explain the possible medication side effects and, especially in females, that the medication not affect weight and/or caused sedation (85).

Many patients are concerned about taking the medications and try complementary therapies instead or use their own techniques to manage headache (32). Patients with migraine are also shown to be interested in treatments for migraine other than those they have already tried (20).

Adherence to non-pharmacological treatment or the patients' experiences is not further studied.

Many studies focus in a quantitative way on evaluating the most effective therapy, but only a few qualitative studies have been conducted to give an in-depth understanding of the experiences of people with migraine (32). Since several studies have shown no differences between migraine treatments (52, 86), the adherence to treatment is low and the burden of migraine is huge, the patients' perspectives on prevention seem important to consider in reducing the burden of migraine.

Exercise and physical activity

Exercise and physical activity are often used as synonyms, but in fact they differ in definition. Physical activity is a broader term defined as any bodily movement produced by skeletal muscles that results in energy expenditure. Exercise, on the other hand, is a kind of physical activity, defined as physical activity that is planned, structured, repetitive, and purposeful in the sense that improvement or maintenance of physical fitness is the objective (3). Physical fitness comprises sets of attributes that people have or achieve that relate to the ability to perform physical activity. The most frequently cited of these attributes can be divided into two groups, one related to health (cardio-respiratory fitness, muscle strength, body composition, and flexibility), and the other concerning to skills that relate to athletic ability (agility, balance, coordination, speed, power, and reaction time).

Effects of exercise

A specific amount of physical activity has been shown to reduce morbidity and mortality from many chronic diseases. The risk for high blood pressure, Type 2 diabetes, and colon cancer is seen to be decreased, as well as the risk for osteoporosis, cardiovascular disease, obesity, and mental ill health (87–88).

Physiological adaptations to exercise are acute responses—the immediate response to a single session of exercise—and chronic responses—how the body responds over time to the stress of repeated exercise sessions. Positive effects of exercise are shown on several parts of the body, such as the heart, skeletal muscles, blood and blood vessels, immune system, skeletal system, cartilage, connective tissues, lungs, body composition, nervous system, skin, stomach-intestinal canal, liver, and hormone system (89). The description of effects of exercise within this thesis will focus on aerobic exercise, which

means exercise that requires effort by the heart and lungs to meet the muscles' increased demand for oxygen (90).

Effects of exercise on the cardiovascular system

As a chronic response to endurance training, increased oxygen delivery to active muscles occurs (90). The functional and dimensional changes in the cardiovascular system induced by aerobic training are a decrease in resting and submaximal exercise heart rate and an enlarged left ventricular cavity. Further signs are enhanced stroke volume and cardiac output and expanded arteriovenous oxygen difference, which is the difference between oxygen concentration in the arteries and the oxygen concentration in the veins.

Effects of exercise on the brain, the central nervous system, and the hormone system

Altered pain perception

Exercise is shown to have a pain modulating effect, both during and after a workout session, which is why it is interesting in the treatment of pain. During exercise, pain thresholds for different kinds of stimulation are higher (91–93). Relive from different pain stimuli are also shown after different kinds of exercise (94–97). There is discussion as to whether physically active people are more pain tolerant than physically inactive people. The former seem to have a higher tolerance to pain, but not always a higher pain threshold (98). Studies have shown an increased pain perception after a prolonged exercise programme in both humans (99) and rats (100), though it is not totally clear whether continuous exercise affects pain tolerance in the long run (101).

The most common theory about pain relief though exercise involves increased levels of endogenous opioids. These can work on different levels, both through the spinal dorsal horn and through central stimulation by means of declining pain-relieving systems (98). An increase of beta-endorphins has been seen during physical activity (102), but the meaning of this for pain relief is still unclear (103).

Increased well-being

Exercise has shown positive effects also on social and psychological health. A cross-sectional study from Finland showed that individuals who exercised at least two to three times a week experienced significantly less depression, anger, cynical distrust, and stress than those exercising less frequently or not at all. Those who exercised at least twice a week also reported higher levels

of sense of coherence and a stronger feeling of social integration than their less frequently exercising counterparts (104).

Several studies have shown that exercise can reduce depression and anxiety, even though more studies on the optimal type, intensity, frequency, and duration are needed (105–106). Depression can lead to increased pain and decreased capacity of pain management. Increased physical activity may influence the pain situation through increased mood. These positive effects are explained through the central serotonergic systems (107). Regular exercise may result in sustaining higher levels of 5-HT, and increased levels have been found both after a single exercise session (107) and as an effect of regular exercise (108). Exercise is also shown to affect cell proliferation in the brain (109), and in patients with depression, a lower hippocampal volume is seen (110).

Apart from the influence on mood, exercise can also break social isolation and increase functional capacity (111). Further, it is shown that the quality of sleep can be improved after regular exercise (112).

The hormone system

During exercise several hormone systems are activated and an increase of, for example, ACTH (adrenocorticotropic hormone), cortisol, epinephrine and norepinephrine are seen (90). As an effect of chronic exercise, the magnitude of hormonal response to a standard exercise level is decreased. The effects on hormones as a response to exercise are summarized in Table 4.

Reduced stress reactivity by exercise

It is supposed that repeated exercise causes a non-specific adaptation, which, according to the 'cross-stressor adaptation hypothesis', may transfer also to psychosocial or cognitive stressors. Exercise entails an activation of the physiological stress regulation, which activates both neural (sympatho-adrenal medullary system) and endocrine pathways (hypothalamic-pituitary-adrenal cortex). Trained individuals show a reduced activation of these two regulation systems during exercise. A high level of fitness also results in improved reactivity under maximal exercise intensity. There is only limited support for the validity of the cross-stressor adaptation hypothesis though. Acute exercise lead to a reduced stress response when stressor tasks follow immediately, but there is not enough evidence to conclude that repeated exercise provokes a general adaptation effect. On the other hand, trained individuals seem to regenerate faster from non-exercise stressors (113), and a negative correlation is found between level of physical activity and perceived level of stress (114).

Table 4 Hormonal responses to exercise, adapted from Katch et al. (90).

HORMONE	RESPONSE TO EXERCISE
Hypothalamus-Pituitary Hormones	
Growth hormone	Resting values increased: trained people tend to have less dramatic rise during exercise
Thyroid-stimulating hormone	No known training effect
Adrenocorticotropic hormone	Trained people have increased exercise values
Prolactin	Some evidence that training lowers resting values
Follicle-stimulating hormone, luteinizing hormone, and testosterone	Trained females have depressed values; testosterone levels may increase in males with long-term strength training
Posterior pituitary hormones	
Vasopressin (ADH)	Some evidence that training slightly reduces ADH at a given workload
Oxytocin	Limited human research available
Thyroid Hormones	
Thyroxine (T_4)	Reduced concentration of total T_3 and increased free thyroxine at rest
Triiodothyronine (T_3)	Increased turnover of T_3 and T_4 during exercise
Adrenal Hormones	
Aldosterone	No significant training adaptation
Cortisol	Trained people exhibit slight elevations during exercise
Epinephrine	Decrease in secretion at rest and same absolute exercise intensity after training
Norepinephrine	
Pancreatic Hormones	
Insulin	Training increases sensitivity to insulin; normal decrease in insulin during exercise is greatly reduced
Glucagon	Smaller increase in glucose levels during exercise at both absolute and relative workloads
Kidney Hormones	
Renin (enzyme)	No apparent training effect
Angiotensin	

A variety of physiological and psychological pathways have been hypothesized to mediate positive effects of exercise also in migraine. Suggestions of such are altered pain perception, increased levels of beta-endorphins and encephalin, increased serotonin activity, and modulation of symptoms thought to precipitate migraine, such as depression and anxiety, response to stress, and improved sleep (115).

Principles of exercise

There are six basic principles of exercise that are essential when conducting an exercise programme and/or interpreting the results of repeated exercise. The principle of *individuality* means that each person is unique and responds to a given exercise programme in different ways. The principle of *specificity* means that 'you improve what you practice', and to maximize the benefits of exercise it must be similar to the type of activity the person aims to improve. Training benefits are lost if training is discontinued or reduced too abruptly, and that is the principle of *disuse*. Furthermore, the training must, according to the principle of *progressive overload*, involve working the body harder than normal, due to the ability of the body to adapt to training. *Hard and easy* means that days of hard training should be followed by a day of easier training for the body and mind to fully recover. Finally, the principle of *periodization* means that in a longer period of training, for example, a year, there should be variations in the intensity, volume, and specific form of training (89).

In 1995 the U.S. Centres for Disease Control and Prevention (CDC) and the American College of Sports Medicine (ACSM) issued a public health recommendation that 'Every US adult should accumulate 30 minutes or more of moderate-intensity physical activity on most, preferably all, days of the week' (88). In 2007, these recommendations were updated and new guidelines for healthy adults under the age of 65 were set. The basic recommendations (Figure 3) are to do moderately intense aerobic exercise 30 minutes a day, five days a week or vigorously intense aerobic exercise 20 minutes a day, three days a week. In addition, strength-training exercises are encouraged twice a week. These sessions are recommended to contain 8 to 10 strength-training exercises with 8 to 12 repetitions of each exercise. Moderate-intensity physical activity means working hard enough to raise the heart rate and break a sweat, yet still being able to carry on a conversation. To lose weight or maintain weight loss, 60 to 90 minutes of physical activity may be necessary. The 30-minute recommendation is for the average healthy adult to maintain health and reduce the risk for chronic disease and premature mortality (116).

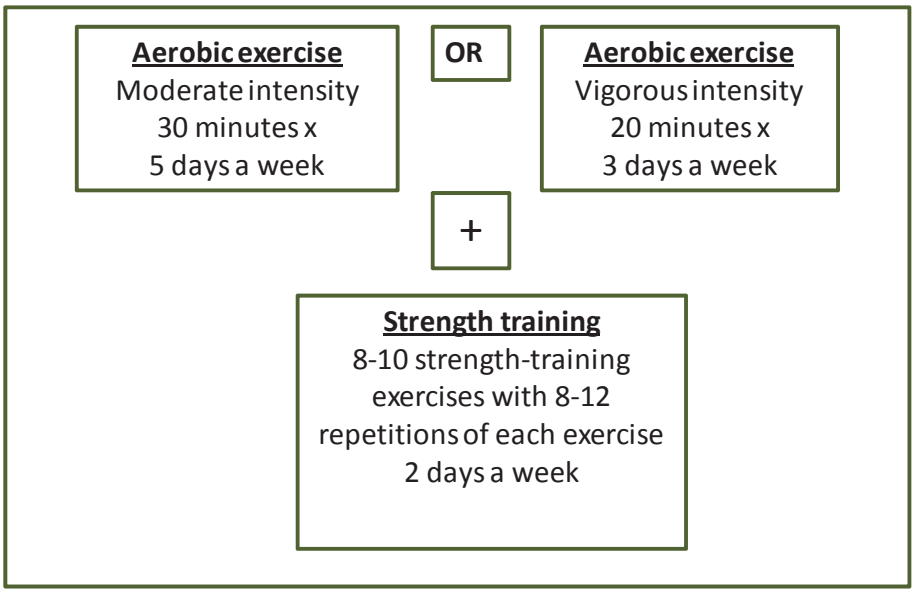


Figure 3 Recommendations for the average healthy adult to maintain health and reduce the risk for chronic disease (116).

Borg's rate of perceived exertion (RPE) scale (117) is a tool commonly used in clinical practice to grade intensity of exercise. This scale was developed according to an existing relationship between a percentage of VO_{2max}, heart rate, and the RPE scale during exercise (Table 5).

Table 5 The RPE Scale (Borg's rate of perceived exertion scale) and the corresponding percentages of maximal heart rate and maximal oxygen uptake (VO_{2max}), adapted after American College of Sports Medicine Position Stand (118).

Intensity of exercise	RPE	Max heart rate %	VO_{2max} %
Very light	<10	<35	<20
Light	10–11	35–54	20–39
Somewhat hard	12–13	55–69	40–59
Hard (heavy)	14–16	70–89	60–84
Very hard	17–19	>90	>85
Maximal exertion	20	100	100

Relations between physical activity/exercise and migraine and other headaches

The knowledge about associations between migraine and physical activity is limited. Some studies have, in different ways, evaluated possible relationships, and their results point in different directions. In a Canadian study of adolescents, migraine did not have a deleterious effect on recreational activity levels (119). Among 344 pupils in a Swedish school aged 13–17, headache was associated with low sports activity in girls, but not in boys (120). On the other hand, in a case-control study done in Germany it was reported that patients with headache had lower aerobic endurance and flexibility than healthy controls (121). The prevalence of migraine was found to be lower among 791 first division basketball players in the USA than in the general population (122). This is also seen among professional soccer players of Italian first-division championship level, where the occurrence of primary headaches appears to be strikingly lower than that found in the general population (123). In a cross-sectional epidemiological study from Denmark (n = 975, 77 with migraine and 167 with tension-type headache (TTH)), no associations between the level of physical activity and migraine were found, but a significantly higher prevalence of TTH was found in men with exclusively sedentary activity (124). This fact was supported by a cross-sectional survey of 12 988 Japanese adults, showing that less walking/exercise as well as sleep problems increased the likelihood of headaches in both genders (125). The relationship between frequency of headache and physical activity has not been clearly described, and there are no prospective studies concerning whether headache can be prevented by physical activity. Increasing this knowledge can be of value both from an individual and a societal perspective.

Exercise in migraine prophylaxis

In a review from 2008, Busch and Gaul evaluated exercise in the treatment of migraine and included available studies and case reports investigating exercise and endurance sports in migraine therapy. Up to now, there have been no meta-analyses or Cochrane Reviews on this specific topic (55). This review included eight studies (126–133) out of which two were abstracts and four case reports. Only two of these were randomized studies. Of the two randomized studies, one studied chronic headache (some of them probably migraine) and the other ‘migraine-like headache’. According to Busch and Gaul, none of these eight studies met valid criteria for good clinical practice (134) and their conclusion was that more studies are imperative to further recommend exercise in migraine based on evidence-based medicine criteria.

Moreover, they conclude that the present grade of recommendation of exercise in the therapy of migraine is B–C.

Difficulties in performing exercise for individuals with migraine

One difficulty for individuals with migraine in doing exercise is that, in the short term, strenuous physical activity can provoke attacks. In a large, clinic-based study, 22% of participants mentioned exercise as a migraine trigger (7). This is one of the reasons some patients with migraine avoid exercise. There are no guidelines regarding how patients with migraine should be instructed to exercise. For this reason, strategies applied for frequency, intensity, and duration of exercise are often those referred to for general health promotion. No studies have been conducted to find the optimal 'dose' for exercise in individuals with migraine, nor have negative side effects been documented and compared to beneficial effects (55).

In a study about management of migraine and chronic daily headache (CDH) (n = 438), avoiding exercise was reported as a prophylaxis management strategy used at least sometimes by 26–33% of patients with migraine and 52% of patients with chronic daily headache (135). On the other hand, prophylactic exercise was also reported as a strategy of migraine management.

Summary of the problem area

In conclusion, migraine is a chronic neurological disorder with immense negative consequences for the individual as well as for society. In the prophylaxis of migraine both pharmacological and non-pharmacological strategies are evidence based. Exercise is often recommended in migraine prevention, but evidence of efficacy is still lacking. It can be difficult for patients with migraine to perform exercise, since heavy physical activity is a well-known trigger for migraine. Since migraine is a chronic disorder that cannot be cured, but merely relieved, prevention is of great importance. It is shown that pharmacological prevention is underused, but the patients' overall views on migraine prevention have not been sufficiently studied. Increased knowledge of the patients' experiences of prevention, as well as evaluating options for migraine prophylaxis are important steps in reducing the burden of migraine.

AIM OF THE THESIS

The overall aim of this thesis was to evaluate different aspects of physical activity in relation to migraine and other headache and possible preventive effects of exercise in migraine treatment. Furthermore, it aimed to elucidate the complexity of migraine prevention from the patient's perspective. The specific aims of the studies were:

- To evaluate, using a prospective design, the relationship between the level of physical activity at baseline and subsequent risk for migraine and non-migraine headache in a long-term perspective (Study I).

- To evaluate the cross-sectional association between physical activity and frequency of migraine and non-migraine headache (Study I).

- To develop and evaluate a method of exercise for untrained patients with migraine (Study II).

- To compare exercise with common pharmacological and non-pharmacological treatments with regard to migraine prevention (Study III).

- To elucidate migraine prevention from the patient's perspective (Study IV).

PATIENTS AND METHODS

The thesis is based on four studies using different methodologies and addressing both quantitative and qualitative aspects of migraine prevention. The studies are listed in Table 6.

Settings

Study I was conducted in Nord-Trøndelag County, which is located in the middle of Norway. The County is mostly rural and sparsely populated; the largest of six small towns has a population of 21,000. In most respects, Nord-Trøndelag County is fairly representative of the whole of Norway, for example regarding geography, economy, and industry, sources of income, age distribution, morbidity and mortality (136). Studies II–IV were conducted in the city of Gothenburg, situated on the west coast of Sweden. Gothenburg is the second largest city in Sweden with approximately 0.5 million inhabitants. The studies were conducted at a specialist clinic, Cephalea Headache Centre, between 2006 and 2009. Study IV was an interview study, and the interviews were conducted at the University of Gothenburg or at participants' workplaces, depending on the participants' preferences.

Table 6 Research design overview.

Study	I	II	III	IV
Aim	To evaluate the relationship between level of physical activity and subsequent risk for migraine and non-migraine headache	To develop and evaluate a method of exercise for untrained patients with migraine	To compare exercise with common pharmacological and non-pharmacological treatments with regard to migraine prevention	To elucidate migraine prevention from the patient's perspective
	To evaluate the association between physical activity and frequency of migraine and non-migraine headache			
Design	Prospective and cross-sectional study	Interventional study	Prospective randomized controlled study	Explorative, descriptive study
Setting	Nord-Trøndelag County in Norway	Headache clinic, Gothenburg, Sweden	Headache clinic, Gothenburg, Sweden	University of Gothenburg or participants' workplaces
Data collection	Questionnaires at two points in time, with 11 years in between	Migraine diaries, VO_{2max}, quality of life formulary	Migraine diaries, $VO_{2max,}$ and quality of life and level of physical activity formularies	Individual interviews
Participants	Part 1. A non-headache population in Nord-Trøndelag County in Norway, n = 33,694	26 untrained patients with migraine with or without aura, with a frequency of 2–8 attacks per month	91 untrained patients with migraine with or without aura, with a frequency of 2–8 attacks per month	21 participants with migraine with or without aura, with a frequency of ≥2 attacks per month
	Part 2. All inhabitants in Nord-Trøndelag County in Norway, n = 92,566			
Analysis	Logistic regression analysis	Wilcoxon signed-rank test	ANCOVA, chi-square, test and Kruskal-Wallis test	Qualitative content analysis

Designs and study populations

STUDY I, was a part of the Nord-Trøndelag Health Study, HUNT, which is one of the largest health studies ever performed, aiming to establish the health history of more than 70,000 people. HUNT includes cross-sectional studies at three different points of time (HUNT 1, HUNT 2, and HUNT 3) between 1984 and 2008. Study I is based on HUNT 1 and HUNT 2 and is an observational study divided into two parts. Part one was a prospective cohort study aiming to evaluate the relationship between level of physical activity at baseline and subsequent risk for migraine and non-migraine headache. Cohort studies can be thought of as a natural experiment in which outcomes are measured in *real world* rather than experimental settings. In these kinds of studies large groups of diverse individuals can be evaluated and followed for long periods, and information on a range of outcomes can be provided (137). Compared to randomized control trials (RCTs), though, there are some disadvantages. The fact that the participants are not randomly allocated increases the risk of selection bias and confounding (138). *Selection bias* means a systematic error in creating intervention groups, causing them to differ with respect to prognosis, and c*onfounding* is a situation in which the estimated intervention effect is biased because of some difference between the comparison groups apart from the planned interventions such as baseline characteristics, prognostic factors, or concomitant interventions (139).

In the prospective part, all inhabitants ≥20 years old in Nord-Trøndelag County of Norway were invited to participate in HUNT 1 (1984–1986) and HUNT 2 (1995–1997). The main purpose of HUNT 1 was to study blood pressure, diabetes mellitus, and factors of lifestyle; 74,599 (88%) of the potential participants underwent a health survey and answered a questionnaire that was sent to them. Questions about level of physical activity were also included in the questionnaire. There were no specific questions concerning headache. However, headache status was indirectly established through a question about the use of analgesics during the previous month, which 59,471 people answered. A total of 41,581 individuals said they had not taken analgesics and were defined as a relatively headache-free population (141–142). Of these, 33,694 were available for the follow-up study, HUNT 2, of whom a total of 22,397 (66%) had answered both the headache questions and at least one of the questions about physical activity in HUNT 1.

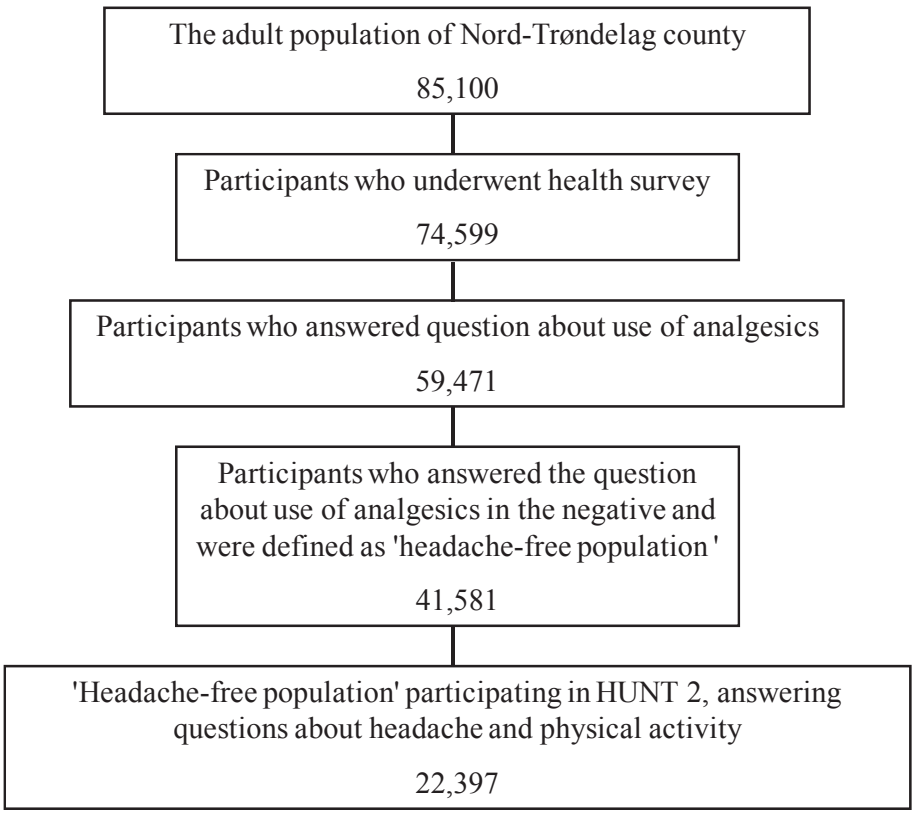


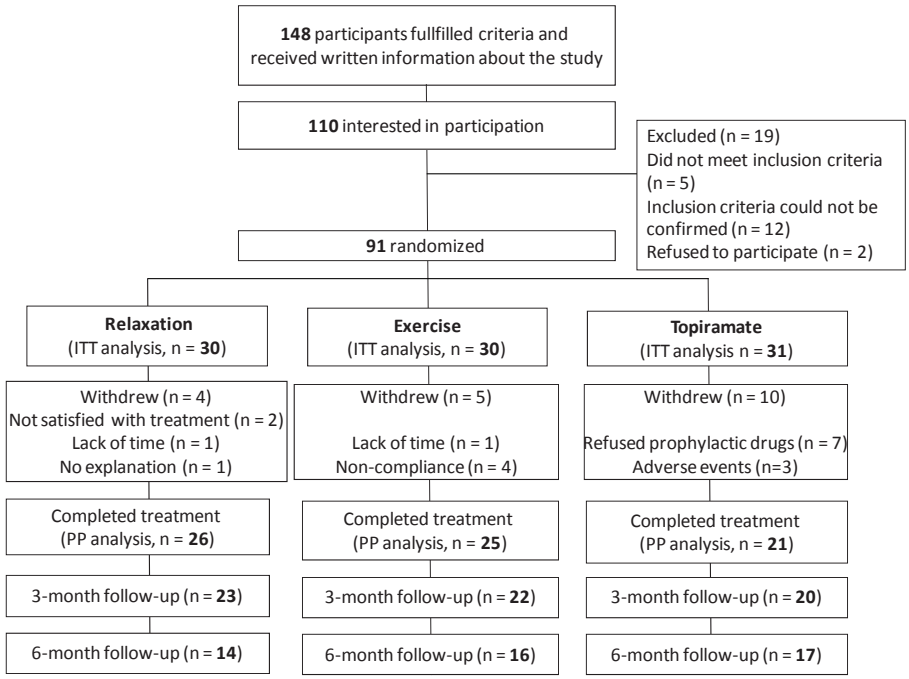
Figure 4 The Study population in the prospective part of Study I.

The cross-sectional part aimed to evaluate the association between physical activity and frequency of migraine and non-migraine headache. A cross-sectional study gives a 'snapshot' of reality. Hence, the relationship between cause and effect cannot be determined, although it can still give a hint important for further studies. The study includes data only from HUNT 2, which was more extensive than HUNT 1 and contained >200 health-related questions, including questions about both headache and level of physical activity. A total of 51,383 (56%) individuals of the 92,566 invited answered the questions about headache. Of these, 46,648 (91%) answered at least one of the questions about physical activity.

STUDY II was an intervention study, which included a baseline period (4–12 weeks) followed by a treatment (exercise) period (12 weeks), and STUDY III was an RCT. RCTs are the best method to use when evaluating treatment effects and are considered the gold standard of true experimental designs. One strength of a randomized study is that potential confounders will be

somewhat similar in the groups, which makes the conclusions from RCTs stronger compared to observational studies (1). Study III included a baseline period of 4–12 weeks followed by an intervention period of 12 weeks, and follow-up was done three and six months after treatment. After the baseline period the participants were randomized into three groups: relaxation, exercise, or topiramate.

The participants were recruited mostly via newspaper advertisements, but also among patients already attending the Cephalea Headache Centre. Twenty-six patients with migraine were recruited and studied in Study II and in Study III 148 patients fulfilled the inclusion criteria, of whom 110 patients were interested in participation and 91 were randomized and included in the study. All patients were examined by a neurologist, and the diagnosis was given according to the criteria of ICHD-II (6). Patients fulfilling inclusion criteria and not fulfilling exclusion criteria for the study were invited by the neurologist to participate in the study. The inclusion criteria were age between 18 and 65 years; migraine with or without aura, with a frequency of two to eight attacks per month; and having had migraine for at least one year before participating in the study and before the age of 50. The exclusion criteria were interval headaches not distinguishable from migraine; medication-overuse headache; regular exercise (≥once per week during the 12 weeks prior to the study); earlier regular practice of relaxation; pregnancy; breastfeeding; use of daily migraine prophylaxis in the 12 weeks prior to the study; inability to understand Swedish; use of antipsychotic or antidepressant medication in the 12 weeks prior to the study; drug or alcohol abuse; and topiramate intolerance.



ITT = Intention to treat
PP = Per protocol

Figure 5 Flowchart for the population in Study III.

STUDY IV was a qualitative study using qualitative content analysis as a method for evaluation. This approach is useful in developing new knowledge about humans' experiences and thoughts. Content analysis was initially developed to deal with quantitative descriptions of communication (142), but has over time expanded to include not only quantitative research but also qualitative research. The quantitative approach is used, for example, in media research, and the qualitative in nursing research and education. According to Krippendorf (4), content analysis is a research method for making replicable and valid inferences from data to their context, with the purpose of providing knowledge, new insights, a representation of facts, and a practical guide to action. The aim of content analysis is to attain a condensed and broad description of a phenomenon, and the outcome of the analysis is concepts or categories describing this phenomenon.

The participants in Study IV were 21 individuals with migraine with or without aura according to the ICHD-II criteria (6), with a frequency of ≥2 attacks per month, debut of migraine attacks at least one year before study

inclusion, and aged between 18 and 65 years. The only exclusion criterion was inability to understand Swedish. The participants were recruited via an advertisement in a high-circulation morning newspaper in Gothenburg, Sweden, and through posters in the waiting rooms of 19 health care centres in different areas of the city. Individuals interested in participation contacted the main investigator, and out of those fulfilling the inclusion criteria, a purposeful sample (143) of 21 individuals was chosen. This was in order to obtain a range of perspectives with regard to gender, age, education level, and severity of disease.

Data collection and evaluations tools

Table 7 summarizes the evaluation tools used in the thesis and studies on reliability and validity.

Table 7 Overview of the evaluation tools and studies on reliability and validity.

Study variable	Instruments	Study	Reliability evaluated	Validity evaluated
Level of physical activity	Questionnaire: HUNT 1	I	X [144]	X [144]
Level of physical activity	Questionnaire: HUNT 2	I	X [145]	X [145]
Level of physical activity	Questionnaire: IPAQ	II–III	X [146]	X [147]
Headache diagnosis: type and frequency	Questionnaire: HUNT 2	I	X [148]	X [148]
Migraine data	Migraine diary	II–III	–	–
Migraine intensity	VAS	II–III	X [149]	X [149]
Quality of life	Questionnaire: MSQoL	II–III	X [150-151]	X [150-151]
Maximal VO_{2max}	The Astrand-Ryhming test	II–III	X [152]	X [153-154]
Patients' perspectives	Qualitative interviews	IV	Not applicable	

IPAQ = International Physical Activity Questionnaire
VAS = Visual analogue scale
MSQoL = Migraine-Specific Quality o Life

Self-reported data on physical activity, headache and non-headache populations (Study I)

As Study I was based on data from questionnaires in the HUNT database, it included self-reported information about physical activity and headache. In HUNT 1, there were three questions about physical activity (frequency, duration, and intensity). A study of young adult men was done earlier to evaluate the reliability and validity of these questions. They were found to

have good reliability in measuring physical activity, with high correlations and mostly good to very good kappa statistics between test and retest. The questions also provide a reasonably valid measure of vigorous activity (144). It is suggested that the answers, can be further divided into the groups 'inactive' and 'active' based on these questions (155). This was done in our study.

In HUNT 2, the questions about physical activity were repeated, but altered in several respects. First, physical activities were measured not only at present, but also during the previous year. Second, participants reported the number of hours per week at different intensities of physical activity, that is, 'light' physical activity (without being out of breath or breaking into a sweat) and 'hard' physical activity (pushing until out of breath or breaking into a sweat). These questions concerned only leisure time. The HUNT 2 question for hard leisure-time physical activity has shown acceptable repeatability and appears to be a reasonably valid measure of vigorous activity when compared with $VO_{2\ max}$, IPAQ (International Physical Activity Questionnaire), and ActiReg (an instrument to measure physical activity and energy expenditure). The light activity question had poor reproducibility and did not correlate well when compared with the other measures (145).

No questions about headache were included in HUNT 1, and headache status at baseline was therefore indirectly defined using information on the use of analgesics. It is assumed that participants reporting 'never' to the question about use of pain-relieving medication during the previous month were unlikely to have headaches, and the proportion of those with headaches would be negligible. This is also done in other studies (141).

HUNT 2 included questions about headache and divided the headaches into migraine and non-migraine. In a study by Hagen et al. (148), the validity and reliability of this self-administered headache questionnaire used in HUNT 2 was made by blindly comparing questionnaire-based headache diagnoses with those made in a clinical interview of a sample of the participants. The results suggest that the self-administered questionnaire may be suitable for identifying a population with 'definite' migraine. TTH is probably the most frequent headache in the group 'non-migraine headache' (156). In a validation study, 80% of non-migraineurs diagnosed with the questionnaire in HUNT 2 suffered from TTH (148).

Data collection: Study I

The data in Study I were collected at two points in time as described in Figure 6. At the first occasion headache-free individuals were identified and frequency, intensity, and duration of physical activity were measured. At the second occasion headache sufferers as well as individuals not suffering from headache were identified, and those with headache were classified into migraine or non-migraine headache. Level of physical activity was measured and divided into low, moderate, and high.

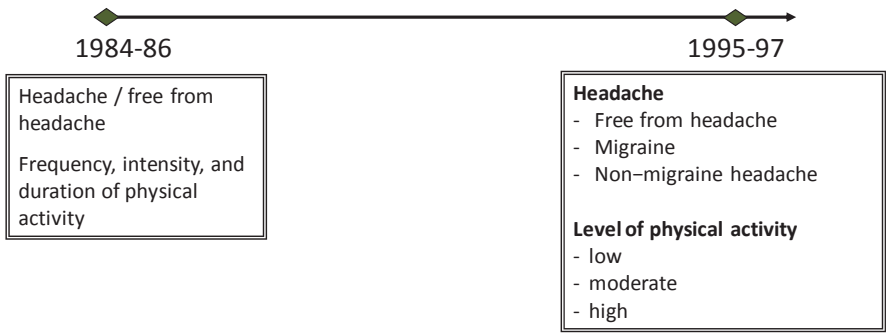


Figure 6 Data collection in Study I was done at two points in time where headache and headache-free individuals were identified, as well as the level of physical activity.

Headache diary (Studies II and III)

A daily diary is seen as 'the gold standard' in the assessment and management of an individual patient (157–158) and preferred over questionnaires or retrospective reports (159–160). Most studies of headache diaries, though, are studies of the diary as a diagnostic tool (158, 161).

According to guidelines for studies of prophylactic treatments in migraine, the evaluation of efficacy should be based on a headache diary, which captures the key assessment measures for the study. The details of the diary design are a local issue, subject to language and culture (162). In Studies II−III a diary based on vertical visual analogue scales (VAS) was used, one for each day to evaluate intensity of pain. The VAS consisted of 100 mm straight lines with 'no pain' as one endpoint and 'worst imaginable pain' as the other (163–164). A vertical VAS incorporated into a pain diary is shown to be valid for prospective registration of pain in headache and non-headache pain (149). The results also demonstrate that pain intensity monitored by a

vertical VAS is both valid and reliable compared with a standard 100 mm horizontal VAS.

Quality of Life (Studies II and III)

In complement to a headache diary, health status and HRQoL can be measured using a generic instrument such the SF-36 (165). Although generic health quality of life instruments are useful in comparing different populations, for some disorders, they may not be responsive enough to detect the minimally important effects of a specific disorder, or inclusive of the specific concerns of patients with this disorder (166). Some instruments are therefore made to measure disease-specific quality of life, and a lack of a migraine-specific measure for assessing ongoing effects encouraged the development of a comprehensive, long-term, migraine-specific quality of life (MSQoL) instrument (167–168).

The MSQoL consists of 20 items, each of which is rated using a response scale with four categories (1 = very much and 4 = not at all). The data can be standardized to a range of values from 0−100, where 0 represents worst health status and 100 represents best health status. The MSQoL instrument was derived from individual interviews and focus group meetings in addition to independent literature reviews (169). In a large international study, the 20-item version of MSQoL met established criteria for validity, consistency, and reproducibility, and showed moderate responsiveness to treatment (150).

Maximal oxygen uptake (Studies II and III)

VO_{2max} is a measure of the maximum amount of oxygen that can be utilized in the body during exercise. The ability to utilize oxygen increases with the level of fitness. Therefore, VO_{2max} is often used to evaluate aerobic capacity. To measure VO_{2max}, is extremely demanding, even for athletes. There are therefore serious practical and ethical concerns in attempting such testing in non-athletic or patient populations (170). An alternative method of measuring exercise capacity in such populations is to estimate VO_{2max} from the heart rate (HR) response to a submaximal rate of work on a cycle ergometer according to the Åstrand–Ryhming nomogram (171−172). This is a much easier way of estimating VO_{2max} when it comes to both equipment and the effort made by the person performing the test. The Åstrand-Ryhming nomogram for cycle has been shown to be reliable and valid (152, 154, 170).

Level of physical activity (Study III)

IPAQ was developed as an instrument for cross-national monitoring of physical activity and inactivity. It estimates the number of minutes per day or

week during which an individual performs different activities. The volume of activity is assessed by weighting each type of activity by its energy requirements, defined as metabolic equivalents (METs), to yield a score in MET-minutes. One MET is a VO_2 of 3.5 mL × kg^{-1} × $min^{-1,}$ which corresponds to the resting metabolic rate, and MET-minutes are the sum of METs for a specific activity multiplied by the minutes performed (173–174). The IPAQ also estimates the number of sedentary hours per day and is shown to be both reliable and valid in an international study made in 12 countries (146). Further it is also shown to have accepted criterion validity for use in Swedish adults (147).

Data collection: Studies II and III

The data in Study II were only collected during the baseline and the treatment period, whereas the data in Study III were collected during baseline, treatment period, and follow-up, as shown in Figure 7.

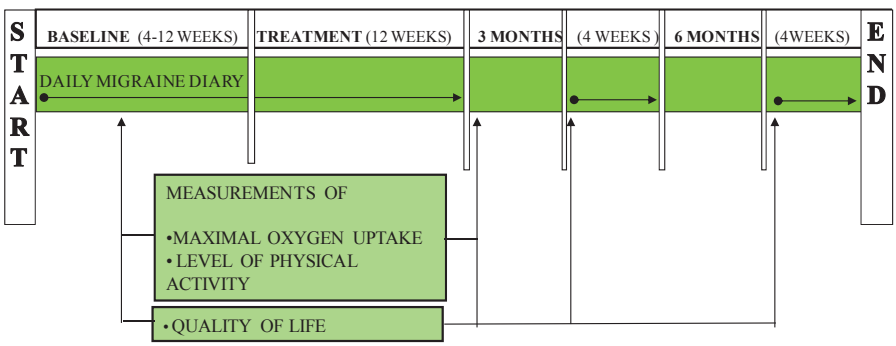


Figure 7 The procedure and data collection at different points in time in Study II and III. Study II included only the baseline and the treatment period.

Interviews (Study IV)

Individual interviews for Study IV were performed with each of the participants using an interview guide (175). This is a tool used in interviews as a reminder of the theme the researcher is investigating, and it ensures that the same line of inquiry is pursued within each interview (176). The interview guide questions were not asked exactly in the same order or manner, as the aim was to have a conversation and to be open to the participant's perspective (177). To start the interviews, an opening question, *How do you perceive that the migraine affects your everyday life?* was intended to build up trust (177). The principal question asked the participants to *narrate their experiences of preventing their migraine*, which allowed

them to raise any issues that they regarded as important on this subject and to gain a deeper understanding of the phenomenon. Further questions were *What are your thoughts when it comes to preventing your migraine?* and *Are there methods for preventing migraine that you are aware of but have no personal experience of?* Follow-up questions were asked to encourage the participants to explain or deepen their statements and to give concrete examples.

Data collection: Study IV

The interviews were conducted during February and March 2011. A majority of the interviews (18 out of 21) took place at the University of Gothenburg and the rest at the workplaces of the participants. This was due to the wish of the specific participant. The surroundings where the interviews took place were in general calm and without disturbance. The data was collected at one point in time with each of the participants. The interviews were performed by a physiotherapist who had no relation to the participants. The interviews were audio-recorded, the median interview time was 31 minutes (range 15–56 min), and they were transcribed verbatim.

Interventions in Studies II and III

Relaxation (Study III)

In the relaxation group, the patients trained individually once a week under the supervision of a registered physiotherapist. The relaxation programme described by Larson and Andrasik (178) was based on progressive and autogenic relaxations techniques (63, 65). They also practised breathing techniques, stress-coping techniques, how to relax during activity, and how to relax in everyday living. They had the chance to discuss the training progress with the physiotherapist and also got written and verbal information before introduction of a new relaxation exercise. The patients received a CD including the six different relaxation exercises, so they could practice daily at home (179). The training was performed in a comfortable, recumbent position lying on the back, sitting in a chair, standing, or walking, depending on the type of relaxation training. In case of absence, they were contacted and given verbal or/and written information about how to continue on their own. For the purpose of the study, adherence to the relaxation treatment was defined as participating in six or more sessions at the clinic, as the programme included six different exercises. Verbal confirmation of practice at home was also required.

Exercise (Studies II and III)

In the exercise group (Studies II and III), the patients trained with a registered physiotherapist three times a week for three months (12 weeks). The exercise programme was based on indoor cycling. The RPE scale was used to set the training intensity (117). Each training session included a 15-minute warm-up period (intensity: RPE scale 11–13), followed by a 20-minute exercise period (RPE 14–16) and a 5-minute cool-down period (RPE 11–13). During the training session, music was included to make the programme more pleasant. The frequency and intensity of training were based on recommendations for increasing VO_{2max} from the ACSM (118) and the authors' clinical experiences of migraine and exercise. All patients had the opportunity to discuss the training with the physiotherapist ad hoc. In case of absence, the patients were instructed to cover that exercise at home or at a local gym. All forms of continuous aerobic exercise (e.g. cycling, jogging, Nordic walking or swimming) were accepted. They were instructed to use the same intensity and duration as in the exercise programme at the clinic. Participants who exercised once per week on average at the clinic and a total of two or more times a week were seen as adhering to the treatment.

Topiramate (Study III)

The topiramate group was an 'active control group'. The patients visited a neurologist before starting the treatment period. They also got written information about the treatment. The dose of the drug was slowly titrated upward, 25 mg every week, to the individual's highest tolerable dose, but not above 200 mg/day. The patients were allowed to call the neurologist any time of the day during the treatment period and also book a time for a scheduled visit if needed. At least one follow-up visit was scheduled. Adherence was defined as using the medicine >2 months in accordance with the prescription and was measured using self-reports (180).

Data handling and statistical methods

The statistical analyses in Studies I and II were performed using SPSS for Windows version 13.0 and 14.0 (SPSS Inc., Chicago, IL, USA). The analysis in Study III was performed using STATISTICA 9.0, StatSoft Inc., Tulsa, OK, USA.

Study I

The influence of physical activity reported in HUNT 1 and HUNT 2 on headache, including migraine, was evaluated using logistic regression

analysis with odds ratio (OR) and 95% confidence interval (CI) as measures of association. Potential confounding was evaluated by adjusting for sex and age. Other potential factors such as education, smoking, level of physical activity at work (cross-sectional study only), and body mass index were also evaluated, but excluded from the final analyses, because they changed the OR by <0.05. When appropriate, headache frequency categories were treated as a continuous variable and incorporated into a two-sided test for trends, to evaluate the probability of a linear relationship between headache frequency and low physical activity.

Study II

The primary measure in Study II was VO_{2max}, since aerobic capacity was studied. Secondary measures were number of migraine attacks per month, days with migraine per month, mean headache intensity, amount of headache medication used, and MSQoL. Wilcoxon signed rank test was used for comparisons (during treatment compared with baseline), since the sample size was small and the data could not be assumed to be approximately normally distributed. A P-value < 0.05 was considered statistically significant.

Study III

A power analysis was conducted in order to detect a clinically relevant difference between the groups in terms of a change in the mean monthly migraine frequency from the baseline, defined as 1.0 attack per month or more. Assuming a standard deviation of 1.2, and a power level of 80%, a two-sided test with an alpha level of 0.05 showed that it was necessary to have 30 subjects in each group.

The null hypothesis in the study was stated as no difference between the three treatment regimes. The hypothesis was used for all efficacy variables. The primary efficacy measure was change in mean monthly migraine frequency from baseline through the last month of treatment.

All data were presented using descriptive statistics, that is, number of observations, mean and standard deviation for continuous variables and frequency and percentage for categorical variables. Continuous data were analysed using ANCOVA, where treatment is used as a fixed factor and baseline levels as a covariate in the model. Data were presented with the least square means and the corresponding 95% CI. The percentage of patients with a reduction compared to baseline of >50%, 25–50% and <25% of the number of migraine attacks during last month of

treatment were analysed using chi-square test. Intensity of pain was measured with VAS and evaluated in two different ways. First, mean and standard deviation were used as descriptive statistics calculated, and then ANCOVA was used to evaluate differences between the groups. In addition, we chose also to evaluate numbers of patients improved or non-improved and compare the groups using chi-square test. When evaluating level of physical activity, a non-parametric test, Kruskal-Wallis, was used, since the data could not be assumed to be approximately normally distributed. All of the tests were two-sided and $P < 0.05$ was regarded as statistically significant.

Intention to treat

The primary analysis in Study III was performed on the intention-to-treat (ITT) population, that is, all patients who met the inclusion criteria and who were randomized to treatment. In the process of analysing, a last observation carried forward technique was used (assuming no change for non-completers) for replacement of missing data. This technique is a conservative means of applying the ITT methodology, with the last value recorded before dropping out carried forward to each missing time period. The assumption was that a patient's score at the time of removal from the study would neither increase nor decrease from that point. All analyses were also done on the per protocol (PP) population, that is, all subjects who did not deviate in any major way from the protocol, including at least one post-baseline measure of the primary efficacy variable and adherence to the actual treatment.

Study IV

The data in Study IV were analysed using a qualitative approach. Each interview was, after transcription, read thoroughly by the first author to get a sense of the content. In the analysis, an inductive approach was used and the data were coded and analysed according to a process described by Graneheim and Lundman (181). This means that meaning units from the texts were marked, condensed, and coded. After that, the codes were arranged in categories. Finally, the latent content was formed into a theme, that is an underlying meaning on an interpretive level.

Ethics

All study populations in the present thesis participated voluntarily. Study I was approved by the Regional Committee for Ethics in Medical Research, and the HUNT study was also approved by the Norwegian Data Inspectorate. Studies II−IV were approved by the Regional Ethics Review Board in Gothenburg. Written informed consent was obtained from all patients, and they were all allowed to withdraw at any point without giving a reason.

Comments on the methodology in Study I

The evaluation tools

A major strength in Study I was the use of valid diagnostic criteria for headache in the cross-sectional part (148). In the prospective part headache status at baseline was indirectly defined using information on the use of analgesics. This is a limitation in the study. To identify a completely headache-free population is, however, difficult, as most subjects will have had headaches during the past year (182), and the way we defined a headache-free population is probably the best possible with the available data. It seems reasonable to assume that the 'analgesic-free' population had relatively minor headache problems compared with the general population. It is, however, reported that some patients with headache do not relieve their pain with medication (183−184). Furthermore, an analgesic-free population probably is an overall healthy population, not just a population free from headache.

Level of physical activity can be measured in many ways. In epidemiological studies self-reported physical activity (PA) questionnaires are the simplest and least expensive method compared with more objective instruments like pedometers and accelerometers (185). Questionnaires about physical activity have a tendency to include recall bias, which can lead to misclassification of individual and population PA habits (186). This is important to consider when interpreting results from these types of studies. The PA measures used in Study I were questionnaire based, although, they were validated and shown to be reliable. It is important to mention that in HUNT 1 the question was about exercise and in HUNT 2 about physical activity, which includes a broader definition. This means that people classified as inactive, that is, who never did exercise, may have practised some other forms of physical activity. On the other hand, using the question about frequency of exercise to classify into two groups, active and inactive, is shown to be reliable and valid in another study of measuring PA (187). The exercise questionnaire in HUNT 1

has been found by others to provide a useful measure of leisure-time physical exercise (144).

Study I, a part of a larger health survey

The material from HUNT used in Study I includes both strengths and limitations. The greatest strength of the study is the large unselected population. A limitation is that the material from HUNT 1 and 2 was collected some years ago (in 1984–1986 and 1995–1997, respectively). The time factor might play a role for the results in these types of epidemiological studies. There may have been some environmental and social changes during the past 30 years. Another limitation is that the survey included two questionnaires, Q1 and Q2, of which Q1 was sent to the participants first. Q2 was sent later and had a lower rate of response. The questions about headache were included in Q2.

Missing data

There were dropouts both in the prospective and in the cross-sectional part. Since the aim of the overall HUNT studies was much more than evaluating possible relationships between headache and physical activity, the questionnaire contained a great number of questions. If the questionnaire in HUNT 2 had included only headache questions, it might have been more likely for the participants to fill out and answer every question. In HUNT 2, a study was done to investigate the reasons that people chose not to participate in the study. A random sample of 685 inhabitants was selected for a non-participation study. This study showed that among people 20–44 years of age, the main reason for not participating was lack of time or having moved out of the country. In the age group 45–69 the main reason was being busy at work, having forgotten the invitation, or just no reason. In the age group of 70 years and above, many reported having regular follow-up by a doctor or hospital, and therefore not needing to attend the health survey. Some reported that they were immobilized due to a disease, and some refused to spend too long waiting at the screening site. A few reported that the health survey was unnecessary or that they were unwilling to participate (136). In the headache part of the study, the head-HUNT, more women (60%) than men (51%) participated. Non-participation was highest among those ≥80 years old (32% participated). Among ‘complete non-participants’ (28,006 subjects), approximately 1,000 subjects had died or moved out of the county before screening. Apart from that, this group was younger (mean age 45.3 years) than the participants (mean age 49.1 years), whereas the ‘partial non-participants’ were slightly older (mean age 50.7 years) ($P < 0.0001$). Judged by the general health questions, a higher proportion of participants reported

good or very good health compared with partial non-participants (72.8% vs. 67.6%, P < 0.0001). However, more specific questions about pain in the neck, shoulder, or back revealed no significant differences between participants and partial non-participants (188). Despite a high dropout, which of course always is a study limitation, the sample size in Study I is still very high.

Comments on the methodology in Study II and III

The evaluation tools

A headache diary has high face validity and provides detailed insight into the characteristics of the headaches, but the use in clinical trials is not without problems. For example, high attrition rates are seen in many trials of prophylactic headache treatments (189), and this might be due to the unwillingness of patients to continually fill in diaries over long periods. The data extraction from headache diaries is relatively straightforward, but still, an important thing to consider when using diaries is that a lot of decisions have to be made about how to handle minor problems (e.g. missing entries for single days or variable headache intensities during a day, etc.) (190). It is therefore also important to use other evaluation tools in studies of migraine prophylaxis, and we chose to complement the headache diary with MSQoL. Further studies on the headache diary as an evaluation tool when it comes to reliability and validity are imperative.

The reason for choosing the MSQoL instead of a generic HRQoL instrument was that MSQoL is shown to be more responsive than, for example, the SF-36 to assessing migraine treatment-related changes (150, 191).

A submaximal test was chosen instead of measuring VO_{2max}, using the gold standard methodology with gas analysis technique. The background of this choice was that Åstrand-Ryhming is much easier to perform, when it comes to both equipment and the effort made by the person performing it. It was also a factor that patients with migraine can develop migraine attacks when performing very strenuous exercise, and we wanted to avoid that.

Methodological divergences between the treatment arms in Study III

The three treatments in Study III differed a bit, which can make it a bit difficult to compare them. First, exercise was in a group and the other treatments were individual. We know that group treatments can have positive

effects, although this is not well studied in migraine. Then, exercise was three times a week and the relaxation was only once a week at the clinic, but the recognition given to the patient individual once a week or in a small group three times a week seems comparable. In the topiramate group the patients mostly met the neurologist two times (or as many times as they needed). The main reason for designing the treatment plans as we did was to reflect the clinical setting as well as possible.

Comments on the methodology in Study IV

There are many different approaches to qualitative research and to meet the aim of Study IV, qualitative content analysis was chosen. The aim of content analysis is described as attaining a condensed and broad description of a phenomenon, and the outcome of the analysis is concepts or categories describing this phenomenon. The focus can be seen as a description of differences and similarities in, for example, a transcribed text (181). Since the method is useful in analyses of a person's or group's experiences, reflections, and attitudes (192) it seemed suitable to use when elucidating the views on migraine prevention from the patient's perspective.

We tried to achieve trustworthiness through credibility, dependability, and transferability (181): In attempt to reach credibility, participants of various genders, ages, severity of disease, and duration of disease were recruited to obtain a richer variation of the phenomena studied. Since everyone including the researcher has a pre-understanding that can influence the interpretation of data, the fact that all three researchers have different occupations and different experiences in migraine strengthens the credibility of the study. Dependability was established, as the main procedures and questions were used in all interviews and almost all of them were made at the same place. The interviews were also conducted within a short period of time. Further, transferability of the study is made possible through a thorough description of the process of analysis, including quotations (Table 13).

RESULTS

Relations between physical activity and headache

Study I showed that individuals who were physically inactive at baseline were more likely to have non-migraine headaches at a follow-up 11 years later (OR 1.14, 95% CI 1.02–1.28). In contrast, migraine tended to be less likely to appear later in life among physically inactive people (OR 0.85, 95% CI 0.70–1.03), but this was not statistically significant. The frequency or duration of exercise showed no relation to migraine or non-migraine headache, whereas high-intensity exercise ('practically until exhaustion') was associated with a higher prevalence of migraine, but not of non-migraine, headache at follow-up. This was only true for women, not for men.

In the cross-sectional part of the study, low physical activity was associated with higher prevalence of migraine and non-migraine headaches. In both headache groups, there was a strong linear trend ($P < 0.001$) towards higher prevalence of low physical activity with increasing headache frequency (Table 8).

Table 8 The cross-sectional part of Study I: Prevalence and odds ratio (OR) of low physical activity related to frequency of headache. Adjusted for sex and age.

	Total number (n)	OR (95% CI)
Headache-free	28,157	1.00
Headache	18,491	
<7 days	14,901	1.16 (1.10–1.21)
7–14 days	2,526	1.25 (1.14–1.38)
>14 days	1,064	1.34 (1.15–1.56)
Migraine	5,840	
<7 days	4,463	1.14 (1.05–1.22)
7–14 days	1,055	1.18 (1.02–1.37)
>14 days	322	1.53 (1.16–2.03)
Non-migrainous headache	12,651	
<7 days	10,438	1.16 (1.10–1.22)
7–14 days	1,471	1.29 (1.14–1.47)
>14 days	742	1.25 (1.04–1.51)

OR = Odds ratio

Evaluation of exercise programme in untrained patients with migraine

Out of the 26 patients included in Study II, 20 completed the treatment period. The reasons for dropout/withdrawal were lack of time (n = 3) and noncompliance with treatment (n = 3). The 20 patients (17 women) were between 36 and 63 years old (median age 49 years). Seven had a migraine diagnosis without aura, one had migraine with aura, and 11 had both diagnoses. The median number of years since the debut of migraine was 32 (range 13–50 years).

After the treatment period, VO2max increased significantly as compared with baseline, 36.2 mL/kg/min vs. 32.9 mL/kg/min (P = 0.044). There was no deterioration in migraine status seen concerning any of the variables evaluated (migraine attack frequency, days with migraine, pain intensity, or amount of headache medication used). On the contrary, during the last month of treatment there was a significant decrease in all these variables as compared with baseline. There was also a significant increase in MSQoL (from 58 to 65 points, P < 0.01) after treatment compared with baseline. The result is presented in Figure 8.

None of the patients reported side effects. In conjunction with the training sessions, on one occasion one of the patients had a migraine attack (migraine with aura), which started immediately after the training session.

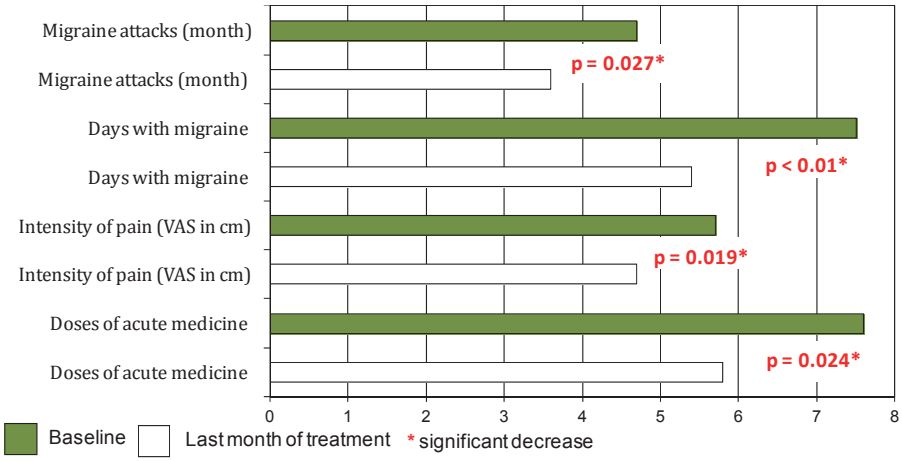


Figure 8 Migraine status during baseline and during the last month of treatment in Study II. Significant decreases are seen among all the variables.

Exercise in migraine prevention

Out of the 148 participants who received written information about Study III, 91 could be randomized and included in the ITT analysis. The flow of participants through each stage of the trial is presented in Figure 5. Among the participants, 44 had migraine without aura, 7 had migraine with aura and 40 had both diagnoses. One of the patients had chronic migraine, that is, migraine ≥15 days/month (6).

Four of the 30 (13%) randomized patients in the relaxation group, 5 of the 30 (17%) in the exercise group, and 10 of the 31 (32%) in the topiramate group withdrew and did not finish the treatment period for different reasons, which also are shown in Figure 5. The PP population therefore included 26 in the relaxation group, 25 in the exercise group, and 21 in the topiramate group. Baseline characteristics of the study population are described in Table 9.

Table 9 Baseline demographic characteristics of the study population in Study III

	Relaxation (n=30)	Exercise (n=30)	Topiramate (n=31)	Total (ITT) (n=91)	Total (PP) (n=72)
Age (years)	41.5 (11.4)	47.0 (10.8)	44.4 (9.2)	44.3 (10.6)	44.4 (11.3)
Sex					
Male	2 (7%)	5 (17%)	2 (6%)	9 (10%)	6 (8%)
Female	28 (93%)	25 (83%)	29 (94%)	82 (90%)	66 (92%)
Weight (kg)	69.8 (9.8)	70.1 (13.3)	75.6 (15.0)	72.1 (13.0)	72.1 (12.7)
Height (cm)	170 (6.5)	170 (8.4)	170 (6.4)	170 (7.1)	170 (6.4)
Body mass index (kg/m^2)	24.1 (2.3)	24.9 (4.1)	26.4 (4.8)	25.1 (3.9)	25.1 (3.9)
Smoking	1 (3%)	2 (7%)	3 (10%)	6 (7%)	5 (7%)
Type of migraine					
Migraine with aura	1 (3%)	3 (10%)	3 (10%)	7 (8%)	5 (7%)
Migraine without aura	16 (53%)	11 (37%)	17 (35%)	44 (48%)	34 (47%)
Migraine with and without aura	13 (43%)	16 (53%)	11 (55%)	40 (44%)	33 (46%)
Duration of disease (years)	22.2 (11.8)	28.8 (11.0)	25.1 (11.4)	25.4 (11.6)	25.7 (11.9)
Migraine days/ month	7.6 (3.8)	7.0 (3.8)	7.5 (3.9)	7.3 (3.8)	7.2 (3.6)
Migraine attacks/ month	4.2 (1.6)	4.3 (2.0)	3.6 (1.6)	4.0 (1.8)	4.1 (1.7)
Headache medication used/month	6.5 (4.6)	6.9 (4.1)	7.1 (5.3)	6.8 (4.6)	7.4 (4.8)
Pain intensity (VAS 0−100 mm)[a]	39 (26−55)	50 (26−64)	40 (29−58)	40 (29−61)	45 (30−63)
MSQoL (0−100 points)[a]	58 (51−67)	60 (43−77)	60 (48−73)	60 (47−72)	59 (50−71)
(Maximal VO_{2max} ($mL \times kg^{-1} \times min^{-1}$)	34.9 (2.4)	33.8 (1.7)	30.9 (2.1)	33.2 (1.2)	32.7 (1.1)

Data are expressed as number (%), mean (SD), or [a]median (interquartile range).
MSQoL = Migraine-Specific Quality of Life
ITT = Intention to treat
PP = Per protocol

Primary efficacy variable

There was a mean reduction in the frequency of attacks per month during the last month of treatment compared with the baseline of 0.93 (95%, CI 0.31–1.54) attacks/month in the exercise group, 0.83 (0.22–1.45) attacks/month in the relaxation group, and 0.97 (0.36–1.58) attacks/month in the topiramate group. No significant difference was observed between the groups (P = 0.95). This result was confirmed in the PP analysis (P = 0.77). An overall test for within-individual changes over time for the entire group showed a significant reduction (P < 0.05). Results regarding changes in attack frequency at different points in time are presented in Figure 9.

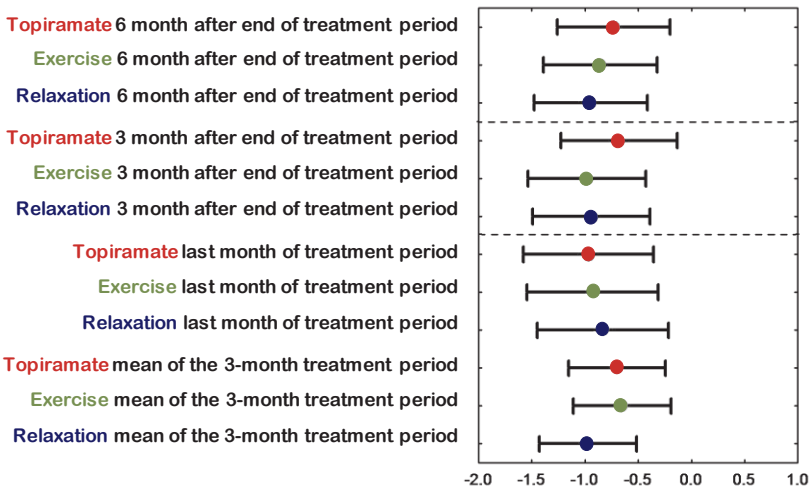


Figure 9 Mean changes from baseline in monthly migraine attack frequency and its corresponding confidence interval within the different treatment groups in Study III.

Secondary efficacy variables

In the exercise group VO_{2max} increased significantly compared with the other groups, +3.9 mL/kg/min compared with 1.1 and -0.4 (P < 0.01). There were no significant differences seen in hours sedentary per day, though. The exercise group had a greater increase in MET-minutes/week (median increase 277 compared with 0 in the other groups), but the result was not significant (P = 0.23).

The improvement in pain intensity from baseline to the mean of the three-month treatment period was significantly higher in the topiramate group (P = 0.04). This was also seen in the PP analysis (P = 0.01), though no differences

were seen when comparing proportions of subjects with a change in pain intensity defined numerically as improved or non-improved (P = 0.29).

No statistically significant differences between the groups were found for migraine days, headache medication used, responders to treatment, quality of life, or level of physical activity at any point of time. A confirmation of all the results were seen in the PP analysis, except for acute medication use six months after treatment. All results are presented in Tables 10 and 11.

Table 10 Results from Study III. Changes from baseline in efficacy variables at different points in time within the groups in the intention-to-treat (ITT) population.

	Point in time	Relaxation	Exercise	Topiramate	P-value
Attack frequency (n/month)	Treatment period	-0.97 (0.23)	-0.65 (0.23)	-0.70 (0.23)	0.57
	Last month of treatment	-0.83 (0.31)	-0.93 (0.31)	-0.97 (0.31)	0.95
	3 months after treatment	-0.94 (0.28)	-0.98 (0.28)	-0.68 (0.28)	0.71
	6 months after treatment	-0.95 (0.27)	-0.86 (0.27)	-0.73 (0.27)	0.85
Migraine days (n/month)	Treatment period	-1.40 (0.43)	-1.15 (0.43)	-1.49 (0.43)	0.85
	Last month of treatment	-1.32 (0.55)	-1.98 (0.55)	-2.13 (0.54)	0.54
	3 months after treatment	-1.47 (0.55)	-2.23 (0.55)	-2.08 (0.54)	0.59
	6 months after treatment	-1.83 (0.52)	-1.71 (0.52)	-1.98 (0.51)	0.93
Mean pain intensity (VAS 0–100 mm)	Treatment period	-3.1 (2.3)	-4.7 (2.3)	-11.1 (2.3)	0.04*
	Last month of treatment	-6.2 (3.2)	-8.8 (3.2)	-14.5 (3.2)	0.18
	3 months after treatment	-5.1 (3.5)	-7.1 (3.5)	-13.7 (3.4)	0.19
	6 months after treatment	-4.6 (3.6)	-5.9 (3.6)	-11.3 (3.5)	0.37
Acute medication used (doses/month)	Treatment period	-1.33 (0.54)	-1.08 (0.56)	-1.89 (0.54)	0.57
	Last month of treatment	-1.56 (0.65)	-1.98 (0.68)	-2.15 (0.65)	0.81
	3 months after treatment	-2.84 (0.54)	-2.72 (0.55)	-2.71 (0.54)	0.98
	6 months after treatment	-2.91 (0.52)	-2.30 (0.53)	-3.64 (0.52)	0.20
Quality of life (points 0–100)	After treatment	3.4 (1.9)	5.7 (1.9)	1.9 (1.9)	0.37
	3 months after treatment	3.1 (2.4)	5.0 (2.3)	2.4 (2.3)	0.73
	6 months after treatment	4.0 (2.2)	5.5 (2.2)	2.5 (2.2)	0.62
Level of physical activity (MET-minutes/week)[a]	After treatment	0 (-453 to 480)	277 (0–1107)	0 (0–403)	0.23
Sedentary (hours/day)[a]	After treatment	0 (-2 to 0)	0 (-2 to 0)	0 (0–0)	0.20
VO_{2max} ($mL \times kg^{-1} \times min^{-1}$)	After treatment	1.1 (1.0)	3.9 (0.9)	-0.4 (1.0)	0.008*

Data are expressed as least square means (standard error) and [a]as median (interquartile range).
*for significant change between the groups

Table 11 Results from Study III. Changes from baseline in efficacy variables at different points in time within the groups in the per protocol (PP) population.

	Point in time	Relaxation	Exercise	Topiramate	P-value
Attack frequency (n/month)	Treatment period	-1.17 (0.25)	-0.66 (0.26)	-0.95 (0.28)	0.37
	Last month of treatment	-1.03 (0.35)	-0.90 (0.36)	-1.27 (0.39)	0.77
	3 months after treatment	-1.15 (0.31)	-0.87 (0.32)	-0.87 (0.34)	0.78
	6 months after treatment	-1.15 (0.30)	-0.80 (0.31)	-0.96 (0.34)	0.72
Migraine days (n/month)	Treatment period	-1.57 (0.60)	-1.89 (0.58)	-3.15 (0.63)	0.16
	Last month of treatment	-1.65 (0.44)	-1.06 (0.45)	-2.2 (0.49)	0.25
	3 months after treatment	-1.75 (0.57)	-2.14 (0.58)	-3.05 (0.63)	0.31
	6 months after treatment	-2.17 (0.53)	-2.03 (0.54)	-2.86 (0.59)	0.55
Mean pain intensity (VAS 0–100 mm)	Treatment period	-3.6 (2.6)	-5.1 (2.7)	-14.9 (2.9)	0.01*
	Last month of treatment	-7.1 (3.7)	-10.2 (3.7)	-20.0 (4.1)	0.06
	3 months after treatment	-5.9 (4.0)	-8.0 (4.1)	-18.7 (4.5)	0.09
	6 months after treatment	-5.3 (4.2)	-7.3 (4.3)	-15.2 (4.7)	0.27
Acute medication used (doses/month)	Treatment period	-1.84 (0.77)	-2.43 (0.82)	-2.94 (0.88)	0.64
	Last month of treatment	-1.59 (0.64)	-1.49 (0.68)	-2.54 (0.73)	0.52
	3 months after treatment	-3.34 (0.59)	-3.10 (0.63)	-3.63 (0.68)	0.85
	6 months after treatment	-3.42 (0.54)	-2.97 (0.57)	-5.02 (0.62)	0.05*
Quality of life (points 1–100)	After treatment	4.3 (2.2)	5.8 (2.2)	2.9 (2.4)	0.68
	3 months after treatment	4.0 (2.7)	4.9 (2.7)	3.7 (3.0)	0.95
	6 months after treatment	4.9 (2.6)	5.1 (2.6)	3.7 (2.8)	0.93
Level of physical activity (MET-minutes/week)[a]	After treatment	20 (-480 to 480)	318 (0–1080)	132 (0–633)	0.34
Sedentary (hours/day)[a]	After treatment	0 (-2 to 0)	0 (-2 to 0)	0 (0-1)	0.32
VO_{2max} ($mL \times kg^{-1} \times min^{-1}$)	After treatment	0.9 (1.0)	4.8 (1.2)	-0.8 (1.2)	0.002*

Data are expressed as least square means (standard error) and [a] as median (interquartile range).
*for significant change between the groups

Adverse events

Adverse events (AEs) were documented by eight patients in the topiramate group (33%). The safety population, that is, patients who took at least one dose of medicine, were 24 individuals. Three of the patients (12.5%) reported AEs as the cause of withdrawal from the study. The AEs reported are listed in Table 12. Some patients often reported more than one type of AE. No serious AEs were reported. No AEs were reported by the patients in the relaxation or the exercise groups.

Table 12 Adverse events in the topiramate group seen in Study III.

Adverse event	Number of patients
Paraesthesia	5
Fatigue	3
Depressed mood	3
Vertigo	2
Infrequent bowel movements	2
Headache	1
Tremor	1
Muscle twitching	1
Mood swings	1
Dysgeusia	1
Nausea	1
Dry eye	1
Epistaxis	1
Dry mouth	1
Urinary incontinence	1
Amnesia	1
Cognitive disorder	1
Diarrhoea	1
Musculoskeletal chest pain	1

Demographics

The weight of the patients was measured before and after treatment. In the PP population, a significant change between the three groups was seen ($P < 0.01$). The mean change was +1.0 kg in the relaxation group, - 0.5 kg in the exercise group and -1.3 kg in the topiramate group.

Preventing migraine from the patient's perspective

The patients' experiences of migraine prevention concerned a difficulty in preventing migraine: knowing whether or not a preventive method or strategy has been effective and how long each strategy should be tried. A general opinion about prevention strategies was that the participants had to pay a price for alleviation. This could involve avoidance of certain things that they enjoyed, enduring side effects of pharmacological prophylaxis, or the need to take a prophylactic medicine on a daily basis. It could also concern struggling with time-consuming, demanding, or expensive non-pharmacological interventions. Two categories about experiences of migraine prevention emerged in different directions, where one was about taking something away, 'Avoiding migraine triggers', and the other one was about adding something, 'Introducing migraine-inhibiting strategies'. Decisions in both of these categories were affected by an appraisal of advantages versus disadvantages, attitudes, support, and knowledge. Increased support and knowledge were requested by the patients. An overarching theme was also developed, 'Migraine prevention from the patient's perspective is a balance between letting it influence life completely and not letting it influence life at all', which encompasses a risk of being controlled by migraine if patients go too far in either of these directions.

Avoiding migraine triggers

The participants' experiences of migraine prevention were dominated by identifying and avoiding potential migraine triggers. This was mentioned by every participant and was sometimes the only strategy of preventing migraine. The participants described that they had searched and were still searching for different factors that triggered their migraine. The avoidance strategy often led to frustration, though, since it was described as difficult to avoid every single triggering factor, and certain triggering factors are by nature impossible to avoid, such as weather changes and hormonal factors. Some participants expressed that despite the long use of avoidance strategies, they still had frequent high migraine attacks.

Introducing migraine-inhibiting strategies

This category was broader since it included a variety of different strategies. The participants described self-care strategies like adding to life things that could increase well-being and things aimed at taking care of oneself. This could be eating nutritious or vegetarian food, increasing physical activity and exercise, doing hobbies like nature photography, or leaving home to spend a

night at a nice hotel. The participants reported that feeling well in body and soul reduces some of the burden of migraine. They also talked about finding balance in life. Furthermore, different preventive interventions, both pharmacological and non-pharmacological methods, were also mentioned and experienced.

A balance between letting it influence life completely and not letting it influence life at all

From the interviews the overarching theme 'Migraine prevention from the patient's perspective is a balance between letting it influence life completely and not letting it influence life at all' was identified. This means that on the one hand, there was a strong desire among the participants to be free from migraine and do everything needed to get better. For some participants, this could lead to negative consequences, like enduring painful treatments, paying a lot of money, and so on. On the other hand, there was an additional strong desire to be normal, to be like everybody else, and to not let migraine and migraine prevention influence life, which instead could lead to an even higher migraine frequency. This theme, and categories exemplified with quotations, are presented in Table 13.

Table 13 Theme, categories, and examples of quotations in Study IV.

Theme: PREVENTING MIGRAINE IS A BALANCE BETWEEN LETTING IT INFLUENCE LIFE COMPLETELY AND NOT LETTING IT INFLUENCE LIFE AT ALL	
Category	**Quotation**
Avoiding migraine triggers	*[I] allow myself to have fun and sometimes go to a cabaret with my friends and then I accept the migraine afterwards, because at least I had a good time in between.*
	It's often things at work and in social life, at home … there are many things that you don't do. I stay around the house. Yes, I try to avoid parties and suchlike, only do what I have to do.
	I kind of know how it works and what causes one and the other. But I have small children and I can't..I can't move away from home so to speak.
	Looking back, you really start to wonder if it [avoiding triggering factors] was really necessary."
	It is the classic with cheese, chocolate and red wine you should avoid. And I have believed in that like everybody else… when I realize that it really isn't true.
Introducing migraine-inhibiting strategies	*But if I knew that it had a preventive effect, I would do anything to get it. Of course, I would obviously not kill for it, but I would do most other things.*
	Of course, if someone had suggested something, like you should try this, some kind of training or relaxation exercises or whatever, something like that, but not more medication.
	Of course, I would have preferred a doctor to manage it and say that we will test this now. And then there will be a follow-up visit after a month or two, thus there is someone who monitors you. Then I know that I have to show a result in two months' time. So if there has been no result, we have to take another route. But as a lay person you grope a bit to find your way, so to speak.
	…[to] have a holiday and enjoy healthy meals and buy good food and things like that, being able to treat oneself and leave the children with somebody else and go to a hotel or … to get away for just one night, to put a gilt edge on one's life or whatever you want to call it. It's also important do something positive, if possible.
	My experience of amitryptiline was that it involved a huge effort, required so much energy to be able to use it. Because … it took a very long time to build up or find your dosage.
	But I don't think that there are any clear directives, as it's a rather fuzzy jungle of different methods, both good and bad.

DISCUSSION

The main findings of the present thesis are that individuals with migraine and other headache are less physically active than headache-free individuals and a high frequency of headache is associated with low physical activity. In patients with migraine, a supervised programme based on aerobic exercise did not deteriorate migraine status; rather, migraine status decreased and VO_{2max} as well as MSQoL increased. Exercise may be an option for the prophylactic treatment of migraine in patients who do not benefit from or do not want daily medication, since the effects were similar to the well-documented methods of relaxation and topiramate with regard to the reduction of migraine frequency. The patients' views on prevention are also important to consider, where the perspective of illness play an important role.

General discussion of the results

Relationships between exercise and migraine

We found that physical activity is negatively correlated with headache frequency. This result is also confirmed in two other recent studies: A Swedish study reported that physically inactive subjects had a higher prevalence of self-reported migraine and/or recurrent headache compared with physically active subjects (193). Inactivity was strongly associated with headache disorders, a finding that could not be explained by economic or psychosocial factors. In a study of 31,865 twins aged 20–71 in Denmark, it was found that the risk of migraine was significantly decreased in participants doing heavy physical exercise not related to work (194). In cross-sectional studies, it is not possible to distinguish between cause and effect. A suggested explanation for this inverse relationship is that people with migraine avoid physical exertion because of its precipitating effect on migraine (195). During attacks of migraine, subjects may also be hindered from performing sports and other physical activities. This explanation may also be true in other studies, which have found that occurrence of primary headaches including migraine is less frequent among athletes (122–123). In the prospective part of Study I, although non-significant, we found the opposite, that physical inactivity at baseline tended to be associated with a lower probability of having migraine at follow-up. The reason is unclear, but this finding may be explained by the fact that physical activity is a well-known trigger, and theoretically, avoiding exercise may reduce the risk of new-onset migraine. On the other hand, we cannot rule out the possibility that the physical activity

studied in the cross-sectional studies have a preventive effect in headache, as seen in migraine reported in Study III.

Effects of exercise in migraine and the optimal way of performing it

Scientific evidence regarding exercise in migraine prophylaxis is required. It was therefore a key finding that there was no significant difference between exercise, relaxation, or topiramate regarding reduction in migraine attack frequency, although, additional studies are needed to verify this result. As we know from previous studies that topiramate and relaxation are effective as means of migraine prophylaxis, we presume that exercise is effective too. This is also suggested earlier (128–130, 196). If the goal is migraine prevention, the preference of the patient is also important, and patients who do not want pharmacological prophylaxis may choose exercise or relaxation. Important from a health perspective, though, is that only exercise gave an increased VO_{2max}, which is closely related to reduced risk for morbidity and mortality (116). Exercise is also shown to be related to less functional disability of migraine (197).

It is possible that the effects of exercise seen in our studies may have been even better, if the patients had chosen the kind of exercise they performed and the time of the day for doing it. We know that some patients found indoor cycling wearying, and also that it sometimes was very stressful to be on time for the supervised exercise sessions. This was probably counterproductive, since stress is a very common triggering factor for migraine (7). To benefit the most from exercise when having migraine, it should be performed according to the preference of the patients. It should be individually supervised to prevent a too high intensity that might trigger migraine attacks, and it may also be important to reduce other triggering factors (such as stress, skipping meals, and so on) in connection with the exercise session. The optimal frequency, duration, and intensity of exercise and choice of exercise method (aerobic exercise, weight training, etc.) are still unknown. Our and other studies have evaluated aerobic exercise (128, 130, 198), and weight training has not been evaluated. When it comes to frequency of exercise, we used three times a week and two times was a limit for adherence in the study. The reason for this was that we wanted to obtain an increased VO_{2max}, and for that purpose exercise once a week is not enough (89). Further studies are needed to show whether there is a potential relationship between increased VO_{2max} and improved migraine status. Knapen et al. (199) studied patients with severe symptoms of depression, which may be of interest also from a migraine perspective. They suggest that exercise

can improve physical self-concept, including physical self-worth, perceived physical strength, and perceived body attractiveness, but an increase in physical fitness was not necessary for those effects.

Our study group comprised untrained individuals. We don't know whether increased exercise frequency also has a migraine preventive effect in patients already doing regular exercise. There is a dose-response relationship shown between physical activity and overall health. To reduce risk for chronic diseases and disabilities, the minimum recommendations are moderate-intensity exercise for 30 minutes five days a week or vigorous-intensity exercise for 20 minutes three days a week, as described earlier. To further reduce this risk, the advice is to exceed the minimum recommendation (116). The exercise programme described in this thesis can be considered comparable to the minimum recommendations. I do not find it as likely that this dose-response relationship is also true in migraine, though, since the level of stress plays a substantial role (200). Exercise affecting the level of stress positively may be most pronounced between low and moderate physical activity (114), but frequent exercise is also described by the patients as stressful. We described several perceived difficulties in doing exercise. It can be experienced as too straining, unpleasant or complicated to perform. One of the patients in Study IV said that exercise could prevent attacks, but being at the gym could also cause attacks, due to, for example, strong smell, which reflects some of the complexity. Further, exercise was shown to have a potentially 'harmful' effect in Study I, by the fact that high intensity of training 'practically until exhaustion' in women was associated with developing migraine later in life. This finding is supported by a study showing a significantly increased risk of migraine with aura in women having a heavy physical work load (194). It seems reasonable to believe that women pushing themselves hard in exercise also push themselves hard in other areas of life and therefore expose themselves to high levels of stress. Stressful life events are suggested to trigger the onset of a migraine headache disorder in some individuals who are predisposed to have migraine (200). In Study IV a break-even point was described for how much one is willing to struggle if the effect is not guaranteed. An example of this was that 20 minutes of exercise, but not 40 minutes was okay for one of the patients. Since migraine is a chronic disease, prevention must be sustained over a long period of time. This is a pedagogical challenge in health care. Based on all the findings within this thesis and my clinical experience, I suggest that exercise in migraine is beneficial, but not too frequent and not too hard, and the importance of individually adjusted exercise should be stressed.

Results from Study III compared with other studies of migraine prophylaxis

We chose a design including active treatments as controls, instead of placebo or 'waiting list'. The issue of placebo-controlled trials has been debated (201), and our decision was based on the conclusion of the Declaration of Helsinki (2008), that a placebo may be used only where no current, proven intervention exists or where there are compelling and scientifically sound methodological reasons (202). A further reason for this design was the need to compare exercise with both standard medical therapy and the most common non-pharmacological option, and the difficulty in placebo control when evaluating exercise. Since we had no placebo group, we cannot, when interpreting the results, exclude that regression to the mean and the natural course of the disorder play a role in the improvements during and after treatment. While the study was randomized, the three groups should, however, have been equally affected. Nor can we, with this study design, determine the relative role of the placebo effect in the different treatment groups. The treatment effects in our study were somewhat smaller than expected, and the effects in the medicine group are smaller compared to other studies of topiramate (45, 203). There are some possible explanations for this. First, in comparison to studies of migraine prevention, our participants were slightly older and had a longer duration of disease (86, 204). Furthermore, we chose not to exclude participants who had severe migraine or those who had failed adequate courses of treatment with ≥3 migraine prophylactic agents. In other studies these are seen as exclusion criteria (204–205). Owing to these factors, our patients may have been treatment-refractory to a greater extent, which may have affected all treatment results negatively. A further reason that the effects seen in our study are inferior to those seen in other topiramate studies could be that we defined ITT more generously. The way in which ITT is defined is not always clear in different studies, and sometimes the definition differs. Therefore, our PP population is more suitable to use in a comparison of treatment effects with the earlier topiramate studies (45–47), some of which only report the PP analysis (203, 206). The efficacy variables and the definition of a migraine attack also sometimes differ. Using the PP population to compare our topiramate group to the earlier pivotal topiramate studies regarding at least 50% reduction of attack frequency, reduction of days with migraine, and if similarly defined, also reduction of migraine attack frequency, shows that our results are superior to the placebo groups in all studies and in some cases superior to the topiramate groups (Table 14) (45–47, 203, 206).

Table 14 Comparison of the topiramate groups from different studies of migraine prophylaxis.

	≥50% improvement	Reduction attacks/month	Reduction days/month
Study III			
topiramate	**PP = 38% (ITT 26%)**	**PP = -1.27 (ITT -0.97)**	**PP = -2.2 (ITT -2.13)**
***Brandes, 2004*[47]**			
placebo	23%	-	-1.3
topiramate 50 mg	39%	-	-
topiramate 100 mg	49%	-	-2.6
topiramate 200 mg	47%	-	-2.9
***Diener, 2004*[46]**			
placebo	22%	-0.8	-1.1
topiramate 100	37%	-1.6	-1.8
topiramate 200	35%	-1.1	-1.3
***Silberstein, 2004*[45]**			
placebo	27%	-	-1.1
topiramate 50	32%	-	-1.6
topiramate 100	54%	-	-2.7
topiramate 200	52%	-	-2.7
***Storey, 2001*[206]**			
placebo	9.5%	-0.55	-
topiramate 100	26%	-1.83	-
***Mei, 2004*[203]**			
placebo	21%	-1.19	-
topiramate 100	63%	-2.66	-

Red numbers = improvement inferior compared to the topiramate group in Study I
Black numbers = improvement superior compared to the topiramate group in Study I
PP = per protocol, ITT = intention to treat

When evaluating treatment effects it is also important to consider whether the improvements seen are clinically relevant. A reduction of one attack/month, which was the average improvement within all groups in our study, is important, since it is comparable to the mean attack frequency in the general population in Sweden (20).

When evaluating quality of life with the MSQoL instrument, five points are regarded as clinically relevant (151). Comparison between the three groups shows that exercise was the only group where a five-point improvement was seen. This improvement was seen at all times of evaluations. The difference between the groups was not significant, but the trend is of interest. We chose to handle data from the MSQoL the same way as the quantitative variables, which can be discussed. This is also seen earlier in studies of topiramate (207). An alternative would have been to compare number of patients with a significant improvement, which may have given other results.

Possible mechanisms for a preventive effect of exercise in migraine

A variety of physiological and psychological pathways have been hypothesized to mediate the effects of exercise in migraine prevention, and most likely, there is a combination of many (115).

In migraine, dysfunction of the opioid system was hypothesized more than 30 years ago (208). Later, reduced beta-endorphin levels were also recorded between migraine attacks (209). An increase of endogenous opioids might therefore affect migraine in a positive direction. A correlation between lower cerebrospinal beta-endorphin levels and severity of disease is also seen (210), and a study of 40 patients showed beneficial effects of exercise on migrainous headache, especially in patients with lower basal beta-endorphin levels (130).

It is suggested that 5-HT play a role in the pathophysiology of migraine. During a migraine attack, the level of 5-HT is decreased. Between the attacks, the level is increased in migraine with aura, but unchanged in migraine without aura (211). Areas in the brainstem, associated with the 5-HT system, are also activated during a migraine attack (212). The documented changes in 5-HT metabolism and in the processing of central 5-HT-mediated responses during and in between migraine attacks, have led to the suggestion that migraine is a consequence of a central neuro-chemical imbalance that involves a low serotonergic disposition (213). The effects on

5-HT of exercise may therefore play a role for its effects in migraine prevention.

The effects on psychological health and improvements of symptoms like depression and anxiety are also important from a migraine perspective. Dittrich (214) aimed in a pilot study to address the influence of an aerobic exercise programme combined with relaxation on pain and psychological variables in migraine patients. A significant reduction of self-rated migraine pain intensity was shown and also an improvement in depression-related symptoms within the aerobic exercise group. The effects of exercise on stress and perceived stress, earlier described, are probably also very important, where a reduced stress reactivity may result in improved migraine frequency. This is shown in a study of the correlation between the frequency of headaches and the frequency of stressful events, which showed that the more a person felt capable of handling stressors effectively, the lower was the observed correlation between headache and stress (215). A negative correlation is also found between level of physical activity and perceived level of stress (114). Furthermore improved sleep may also play a role in improvement of migraine frequency, since sleep disturbance also is a common triggering factor.

The patients in our qualitative study also used exercise as a strategy in migraine management. The participants described exercise in both positive and negative terms, but among the positive effects, not only reduction of migraine was described but also an increased well-being. A study of exercise in patients with late effects of polio confirms the finding that it appears that the experienced effect of group training goes beyond improving physical functions (216).

Migraine prevention from the patient's perspective

Evidence-based treatment is fundamental in health care. This can be described as using the current best evidence in making decisions about the care of individual patients (217). The practice of evidence-based medicine includes an integration of individual clinical expertise and the best available external clinical evidence from systematic research. Furthermore, the individual patient's choice should also be considered. Because of this, the patient's perspective as well as evaluation of treatment effects is of importance in research about prevention.

We found that the patients' views on migraine prevention could be described as a continuum between letting it influence life completely and not letting it influence life at all. A risk of being controlled by migraine by going too far in either of these directions was identified. The risk of letting it influence one's whole life was seen through a high degree of avoidance or through an uncritical use of preventive methods, both resulting in too many negative consequences. The opposite risk was in not avoiding obvious triggering factors or not using preventive therapy, due to different reasons concerning disadvantages, attitudes, lack of support, or lack of knowledge, leading to an even higher migraine frequency. Based on our results, we hold that acceptance of the disease and recognition that migraine prevention will influence life to some degree is a way for the individual to take control (Figure 10).

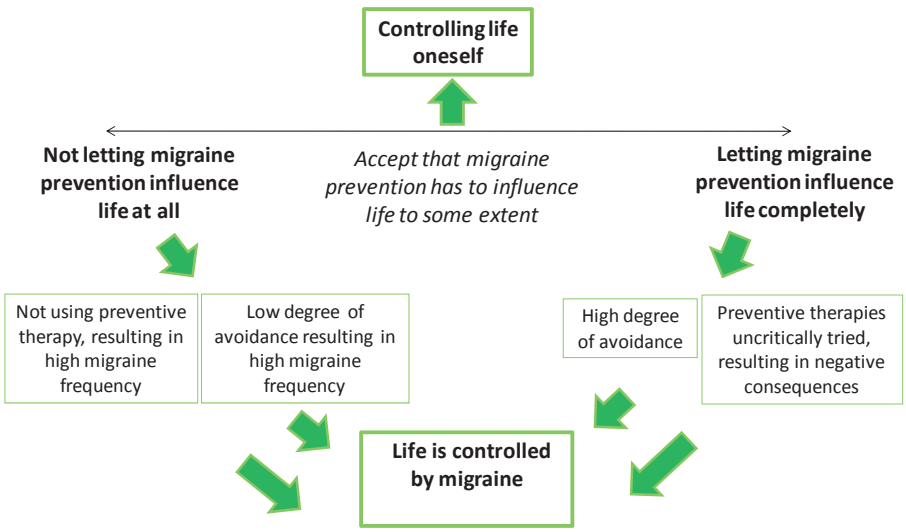


Figure 10 Migraine prevention from the patient's perspective can be seen as a continuum between not letting migraine influence life at all and letting it influence life completely, which in both directions can lead to a life controlled by migraine. Through acceptance of the disease and the understanding that prevention has to influence life to some extent, it is possible for the individual to take control.

Perceived control over the effects of pain on activity and role functioning are suggested to be more adaptive than control over the pain itself (218). This is also what we mean by controlling life oneself. This means that the patient may have to accept that everything is not controllable, which is also suggested earlier in studies of chronic pain (219–220). The importance of acceptance and trying to balance between managing the disease and maintaining wellness through continuing important things in life is earlier described as a balance between illness and wellness (221). The same struggle was evident in our interviews. This is an important finding, as it is not only a struggle to convince patients to adhere to a specific treatment; it is also a risk when they try too hard to free themselves from the disease.

The Shifting Perspective Model of Chronic Illness (33) describes a process in line with what we have found. The illness in the foreground perspective dominates in patients who are letting migraine prevention influence their lives completely. The opposite perspective, with wellness in the foreground, is positive, but includes a risk of ignoring the disease, possibly contributing to deterioration. In our study this is shown as not letting migraine prevention influence life at all. When living with wellness in the foreground, sickness is distant, but still the disease must be managed. This includes the necessity for the person to recognize the disease as a fact of life, while at the same time rejecting the limitations and significance of it. We describe this as a recognition that migraine prevention will influence life to some degree, which is a way of taking control oneself. The patient's perspective of illness is thus important in migraine prevention, since it affects how patients think regarding preventative treatments. It is also important to know that the perspective can change, which may explain why the same patient on the one hand wants to do everything in order to get better, and on the other hand, at another point in time, not want to pay the price to prevent migraine. The change in perspective may shift from wellness in the foreground to illness in the foreground, if the illness gets worse (33). In migraine the perspective may change during and between attacks. The experience of chronic illness is individual, and patients in either perspective need to be supported.

We have also described that there is a price to pay to prevent migraine. This is something that the patient must understand. Moreover, the choice of strategies or therapies the patient wants to use in prevention is personal, which must be considered when giving advice to the individual patient. It is also essential to recognize that not all patients prefer the same approach to care, nor will the same individual necessarily prefer the same approach in all phases of care and rehabilitation (222). Studies have shown that some patients do not wish to actively participate in making treatment decisions

(223–224), and even if they are seeking knowledge about treatment options and want more information, not all patients want to choose among the treatment options (225–226). Our study confirms that patients also differ as to how much and in what way they want prevention of the disease to influence their lives. To take the patient's perspective of the illness into consideration as well as finding the most suitable treatment is important to meet the needs of the individual person and to improve health care.

The greatest problem as I see it, however, is that effective preventive therapies remain untried by the migraine sufferers. Howsoever effective a treatment method is, it is not effective if the patients do not know of it or for other reasons do not use it. It was an overall opinion among participants in Study IV that there was lack of knowledge about effective treatment strategies, as well as difficulty knowing whether a method had been effective or not. Patients with frequent migraine need increased knowledge as well as support. Knowledge and support are also shown helpful in keeping wellness in the foreground perspective (33).

Study IV also confirmed that there exists an opinion against prophylactic medication, which makes non-pharmacological treatments important. However, there are some negative consequences associated with non-pharmacological treatments also. A common opinion was that these interventions often are time-consuming. Time-consuming interventions were not preferred by some patients, since the migraine itself takes so much time. Our results are supported by an earlier study of patients with migraine and CHD that described the patients adapting headache management to suit their needs and preferences, which makes management highly individual and means that patients play a central role in their own care. Assessing and recognizing a patient's readiness for change may therefore be important in prevention, not least when introducing non-pharmacological treatments (227).

A treatment plan comprising strategies to optimize adherence could begin by assessing and addressing the patient's perception of the risks and benefits of an intervention (51). Adherence is likely if the patient believes that the benefit is great and the risks low, whereas if he/she believes that the risks are high and the benefits low, adherence is very unlikely (51). Based on our findings, the term *effort* involved in a treatment could be used instead of *risk* in relation to non-pharmacological methods. This covers the investment of time in the treatment, short-term stress, and negative feelings. When choosing a form of treatment, such informed consideration is important. Adherence may be increased by helping the patients to obtain knowledge about the

potential benefits of a given treatment and through support during the intervention period (180).

Migraine prevention from the physiotherapist's perspective

The importance of the physiotherapist's role in migraine prevention can be seen based on the results from the studies within this thesis. Low physical activity is correlated to a higher frequency of headache, and inactivity may lead to the deterioration of many of the body functions as well as to poor health (228). Increasing physical activity in patients with headache is therefore important in helping them to maintain good health. This task is fundamental in physiotherapy. There may, as earlier stressed, also be a need of tailored exercise to increase adherence, since exercise is described as difficult for patients with migraine. Some patients with migraine prefer non-pharmacological options and exercise as well as relaxation may be alternatives to pharmacological prophylaxis, which also strengthens the role of a physiotherapist in migraine prevention. The patients request someone who can follow up treatment and evaluate its effects. Increased knowledge and support are also requested, and counselling and education are important parts of the work of a physiotherapist (40). According to the Shifting Perspectives Model of Chronic Pain, rehabilitation is not about the patient accepting losses and limitations imposed by the disease. Instead it should be seen as an opportunity for transformation and a help in holding the perspective of wellness in the foreground. A fundamental characteristic of physiotherapy is that individuals have the capacity to change as a result of their responses to physical, psychological, social, and environmental factors. Body, mind, and spirit contribute to individuals' views of themselves and enable them to develop an awareness of their own movement needs and goals (36). This also strengthens the role of a physiotherapist in chronic illness such as migraine, helping the patients taking charge of their own resources (Figure 11). In summary, there are many areas where migraine prevention could potentially benefit by including a physiotherapist, even though there is a lack of evidence for 'physiotherapy' in the literature (42).

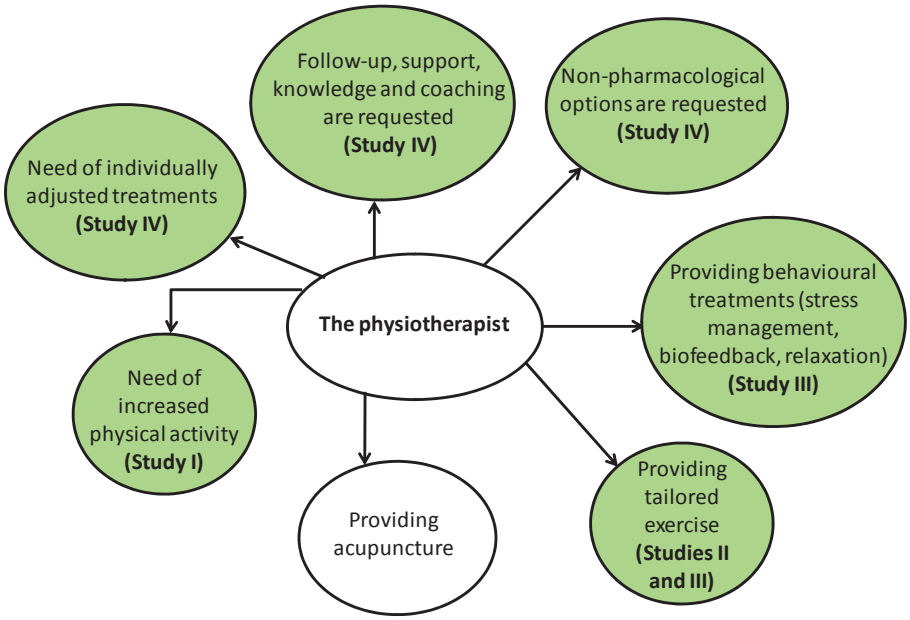


Figure 11 Based on the findings within this thesis, the role of a physiotherapist as part of the rehabilitation process for patients with severe migraine is of great value and can contribute to holding a perspective of wellness in the foreground and finding and providing suitable non-pharmacological management strategies.

Gender perspective of the thesis

It may also be of interest to look upon the thesis from a gender perspective. It is known that women have higher migraine prevalence than men. Nausea and/or vomiting are also more common in women (17). Further is it shown that the severity of migraine pain, and also pain in temporomandibular disorders and fibromyalgia, varies with the menstrual cycle, peaking around the time of menstruation when both oestrogen and progesterone are lowest (229).

In Study IV we used a purposeful sample to get as broad as possible a description of the patient's perspective, and therefore we included a representative proportion between men and women. When it comes to experiences of, and how to think regarding prevention, of migraine, these may vary between men and women, and therefore using such sample is a strength in our study. The studies in this thesis, though, do not speak to gender differences in views on prevention. Neither can we clarify whether the response to treatment varies between genders, which would have been

interesting to know. However, the finding of this thesis that exercise as well as relaxation may be an option in migraine prevention is perhaps especially important for women of fertile age. The reason for this is that pharmacological prophylaxis may be contraindicated if they are trying to be, or already are, pregnant or breastfeeding.

We found a difference between men and women in Study I. It was shown that in women, but not in men, training 'practically until exhaustion' was associated with an increased risk of developing migraine later in life. This may have to do with different reactions to stress between men and women. Men have been shown to benefit more from physical activity while under stress than women (230), which may be due to the 'fight-or-flight' response to stress, which is proposed to be stronger in men, whereas a 'tend-and-befriend' response is more common in women (231). This may have affected the response to exercise also in our studies. With a larger study group it might be possible to do such subgroup analyses.

Generalizability and clinical relevance of the thesis

Generalizability of the results is important in order to transfer the findings from research to clinical practice. A major strength of Study I is the high generalizability, since all inhabitants in Nord-Trøndelag County were invited to participate. The dropout rate is a limitation, however, which is discussed earlier. Studies II and III are based on a self-selected sample of patients, and the external validity is therefore not obvious. In an attempt to increase the generalizability of our findings, participants were predominately recruited via newspaper advertisements and not only from a specialist headache clinic. The studies excluded patients who already undertook regular exercise, which could affect the external validity, but in Study I, migraine sufferers were found to exercise less with increasing severity of the disease. Regarding MSQoL, the patients in Study III were comparable to patients with migraine in a large study of 1,383 patients (150). The studies included a slightly higher proportion of women (Study II 85%, Study III 90%) in comparison to migraineurs in Sweden (77%) (20). Regarding the frequency of attacks, we included patients with a migraine frequency of 2–8 migraine attacks per month, but in the general population mean attack frequency is 1.3 per month (17). This shows that our study population were more troubled by migraine than a migraineur in the general population, but on the other hand, not all migraineurs in the general population need prophylactic treatment.

The dropout rate during Study III was an issue. It is known from earlier studies, that participants often have a preference for drug or behavioural therapy and this preference may undermine adherence, influence dropout rate, and even affect treatment response (232–233). We know that this was the fact for some of the patients, who entered the study and wanted to be in the exercise group. Some of these dropped out when they were randomized to topiramate. This can make the results for the topiramate group unfair, but since we analysed both using intention to treat and per protocol and there were no differences in the results, this problem should have been controlled for. Patient dropout because the patient expects to receive another treatment is also shown in other randomized controlled studies comparing non-pharmacological treatment with pharmacological. In a study comparing metoprolol and acupuncture, about a third of the patients randomized to metoprolol did not complete (204). In our study there were not only drop-outs in the topiramate group, though. For ethical reasons, participants were assured the right to drop out at any time without giving a reason. The total proportion of patients completing our study per protocol was higher than what is seen in other studies of topiramate in migraine prophylaxis (45–46).

The sample size in Study III was somewhat small, but since a power calculation was done and a sufficient power was achieved, it is reasonable to believe that the results are true. No significant differences between the treatment groups were found, but it cannot be concluded that differences do not exist. It seems, however, logical to argue that if there were a clinically relevant difference, it would have been revealed, and if there were differences too small to discover with this sample size, factors other than effect may be important to consider when choosing prophylactic treatment. Based on the discussion above, it is suggested that the findings from Studies II and III can be valid for untrained migraineurs in Sweden, with frequent migraine in need of prophylaxis.

Since Study IV was qualitative, the aim was not primarily generalizability. With the relatively small sample size is it not sure that all aspects of migraine prevention could be captured. The participants were recruited via advertisement, which also can lead to a potential bias in recruitment, in that the participants might be more enterprising than others. We included people who had at least two migraine attacks per month, since that frequency is suggested as one of several indications to start using migraine prophylaxis (43). We therefore included participants who had obtained insufficient relief from treatment and excluded patients who so successfully managed to prevent their migraine that they had less than two attacks per month. We thus believe this study group is representative of those seeking or needing health

care for migraine. In general, a qualitative research approach does not attempt to generalize the findings to a whole population, but rather to develop new knowledge about human experiences and thoughts. According to Krippendorf (4), a text never implies one single meaning, just the most probable meaning from a particular perspective. The interpretation made in our study should therefore be considered as one possible interpretation of the views on migraine prevention. It is likely, though, that the different aspects within the categories and theme identified in our study can be identified also in other patients with migraine.

CONCLUSIONS

In this thesis several epidemiological relationships between physical activity and headache were investigated and described. A method of exercise for patients with migraine was developed and evaluated through a comparison with common pharmacological and non-pharmacological treatments in the prevention of migraine. Furthermore, the patients narrated their views on migraine prevention, which provided increased knowledge about migraine prevention from the perspective of the sufferers. The findings altogether support that the physiotherapist has a role in the prevention of migraine, not only in tailored physical activity and exercise but also in giving support and providing non-pharmacological treatment options adjusted to the preference of the individual patient.

The conclusions based on the four studies are that:

- Total inactivity among headache-free individuals may increase the probability of developing non-migrainous headache later in life.

- Individuals with migraine and non-migraine headache are less physically active than those without headache, and there was a strong linear trend of higher prevalence of 'low physical activity' with increasing headache frequency.

- An exercise programme based on indoor cycling (continuous aerobic exercise), including warm-up and cool-down periods, is shown to improve VO_{2max} in untrained migraineurs, without increasing their migraine status.

- The effects of exercise did not significantly differ in comparison of efficacy with common and well-documented pharmacological and non-pharmacological migraine prophylaxis. Increased VO_{2max} was seen in exercise, and side effects were seen only in the pharmacological group. The findings suggest that exercise may be an option for the prophylactic treatment of migraine in patients who do not benefit from or do not want daily medication.

- Within the patient's perspective on migraine an important balance is described between letting it influence life

completely and not letting it influence life at all, which in either direction can lead to a life controlled by migraine. Accepting the disease and accepting that migraine prevention must influence life to some degree is a pragmatic way of taking control oneself.

- The patient's perspective of the illness influences decisions about migraine prevention. Both avoiding migraine triggers and introducing migraine-inhibiting strategies are described; these are dependent on an appraisal of advantages versus disadvantages, attitudes, support, and knowledge. Increased support and knowledge are requested by the patients.

FUTURE IMPLICATIONS

Several issues have arisen during this study process, which may lead to further investigations.

- Additional studies are needed to verify the results of exercise as migraine prophylaxis.

- Exercise is evaluated in adults, but not in adolescents, which is of interest, because prophylactic medications are not as well-evaluated in adolescents and there is a need for further treatment options for this patient group.

- There is still a lack of knowledge about the optimal way to perform exercise in migraine prevention. Further studies may compare different types of exercise and evaluate different frequencies, durations, and intensities of training. Is there a dose-response relationship?

- Exercise is studied in migraine prophylaxis, but still there is only anecdotal evidence that exercise also has an acute effect on migraine. This is something to study further.

- Is there a difference in response to exercise between men and women with regard to migraine prophylaxis?

- Was the increased VO_{2max} important for the preventive effect shown in Study III?

- We suggest in Study IV that accepting migraine and the fact that preventing migraine must influence life to some degree is a way of taking control. This may be something to further study and relate to quality of life.

- Patients with migraine are requesting increased knowledge and support. It would be interesting to investigate whether increased knowledge and support could lead to increased quality of life and reduced migraine frequency.

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