The effects of aerobic exercise and the impact of migraine and co-existing tension-type headache and neck pain

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The overall aims of this thesis were to investigate the effects of an aerobic exercise program and the impact of migraine and co-existing tension-type headache (TTH) and neck pain (NP) in persons with these combined conditions. This thesis is based on four studies.

In study I, a new questionnaire, Impact of Migraine, Tension-Type Headache and Neck Pain (Impact M-TTH-NP), was developed. This questionnaire covered pain, triggers, psychosocial, socioeconomic and work related aspects. Face and content validity were investigated together with five additional questionnaires; the International Physical Activity Questionnaire (IPAQ short form), Migraine-Specific Quality of Life Questionnaire (MSQ v. 2.1), The World Health Organization five-item Psychological Well-Being Index (WHO-5), Major Depression Inventory (MDI) and Neck Disability Index (NDI). Face validity was assessed by group interviews of nine persons with migraine and co-existing TTH and NP. Content validity was assessed by the degree of relevance by 13 headache experts. Impact M-TTH-NP showed acceptable face validity and excellent content validity. MSQ, WHO-5, MDI and NDI showed acceptable face validity, and WHO-5, MDI and NDI showed excellent content validity.

In study II, the prevalence of co-existing TTH and NP in a clinical sample of persons with migraine was investigated. Also, we investigated level of physical activity, psychological well-being, perceived stress and self-rated health in persons with migraine and co-existing TTH and NP, their perceived ability to engage in physical activity and which among the three conditions (migraine, TTH or NP) was rated as the most burdensome condition. A survey of 148 persons with migraine and 100 healthy controls was conducted. The prevalence of co-existing TTH and NP in persons with migraine was 67%; this group had a low level of physical activity, low psychological well-being, high level of perceived stress and poor self-rated health compared to healthy controls. They reported reduced ability to engage in physical activity owing to migraine (high degree), TTH (moderate degree) and NP (low degree). The most burdensome condition was migraine, followed by TTH and NP.

In studies III and IV, the effect of a 12-week aerobic exercise program, with follow-up six months from baseline, in persons with migraine and co-existing TTH and NP was investigated in a prospective, open-label, randomized, clinical trial. Fifty-two persons (26 in exercise group and 26 in control group) completed the six-month study period. The exercise group showed a significant improvement in the ability to engage in daily activities because of reduced impact of migraine compared to controls. Migraine frequency, pain intensity and duration were significantly reduced in the exercise group compared to baseline, although not significant compared to the control group (Study III). The effect of the aerobic exercise program on pain perception was measured in Study IV. We did not identify any significant effect on muscle tenderness and pain thresholds. We concluded that aerobic exercise had positive effects on migraine severity and migraine burden, but these results could not be explained by the applied tests of muscle tenderness and pain thresholds. Thus, the positive effect on migraine burden may rather be explained by positive alteration of avoidance behaviour.

Key words: migraine, tension-type headache, neck pain, aerobic exercise, impact, pain perception, validation

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Abstract

The overall aims of this thesis were to investigate the effects of an aerobic exercise program and the impact of migraine and co-existing (tension-type headache) TTH and (neck pain) NP in persons with these combined conditions. This thesis is based on four studies.

In study I, a new questionnaire, Impact of Migraine, TTH and NP (Impact M-TTH-NP), was developed. This questionnaire covered pain, triggers, psychosocial, socioeconomic and work related aspects. Face and content validity were investigated together with five additional questionnaires; the International Physical Activity Questionnaire (IPAQ short form), Migraine-Specific Quality of Life Questionnaire (MSQ v. 2.1), The World Health Organization five-item Psychological Well-Being Index (WHO-5), Major Depression Inventory (MDI) and Neck Disability Index (NDI). Face validity was assessed by group interviews of nine persons with migraine and co-existing TTH and NP. Content validity was assessed by the degree of relevance by 13 headache experts. Impact M-TTH-NP showed acceptable face validity and excellent content validity. MSQ, WHO-5, MDI and NDI showed acceptable face validity, and WHO-5, MDI and NDI showed excellent content validity.

In study II, the prevalence of co-existing TTH and NP in a clinical sample of persons with migraine was investigated. Also, we investigated level of physical activity, psychological well-being, perceived stress and self-rated health in persons with migraine and co-existing TTH and NP, their perceived ability to engage in physical activity and which among the three conditions (migraine, TTH or NP) was rated as the most burdensome condition. A survey of 148 persons with migraine and 100 healthy controls was conducted. The prevalence of co-existing TTH and NP in persons with migraine was 67%; this group had a low level of physical activity, low psychological well-being, high level of perceived stress and poor self-rated health compared to healthy controls. They reported reduced ability to engage in physical activity owing to migraine (high degree), TTH (moderate degree) and NP (low degree). The most burdensome condition was migraine, followed by TTH and NP.

In studies III and IV, the effect of a 12-week aerobic exercise program, with follow-up six months from baseline, in persons with migraine and co-existing TTH and NP was investigated in a prospective, open-label, randomized, clinical trial. Fifty-two persons (26 in exercise group and 26 in control group) completed the six-month

study period. The exercise group showed a significant improvement in the ability to engage in daily activities because of reduced impact of migraine compared to controls. Migraine frequency, pain intensity and duration were significantly reduced in the exercise group compared to baseline, although not significant compared to the control group (Study III). The effect of the aerobic exercise program on pain perception was measured in Study IV. We did not identify any significant effect on muscle tenderness and pain thresholds. We concluded that aerobic exercise had positive effects on migraine severity and migraine burden, but these results could not be explained by the applied tests of muscle tenderness and pain thresholds. Thus, the positive effect on migraine burden may rather be explained by positive alteration of avoidance behaviour.

Summary in Danish (Dansk sammenfatning)

De overordnede mål med denne afhandling var at undersøge effekten af konditionstræning til personer, der lider af migræne, spændingshovedpine og nakkesmerter, og hvordan denne gruppe er påvirket af disse kombinerede tilstande. Afhandlingen består af fire studier.

I studie I blev et nyt spørgeskema udviklet, "Påvirkning af Migræne, Spændingshovedpine og Nakkesmerter", som dækker smerter, triggerfaktorer, psykosociale-, socioøkonomiske og arbejdsrelaterede forhold. Derefter blev face- og indholdsvalidering af det nyudviklede spørgeskema testet sammen med yderligere fem spørgeskemaer: The International Physical Activity Questionnaire (IPAQ short form), Migraine-Specific Quality of Life Questionnaire (MSQ v. 2.1), The World Health Organization five-item Psychological Well-Being Index (WHO-5), Major Depression Inventory (MDI) and Neck Disability Index (NDI). Face-validering blev vurderet ved gruppeinterview af ni personer med kombinationen af migræne spændingshovedpine og nakkesmerter. Indholdsvalidering blev vurderet ved graden af relevans af 13 hovedpineeksperter. Det nyudviklede spørgeskema viste acceptabel face-validitet og fremragende indholdsvaliditet. MSQ, WHO-5, MDI og NDI viste acceptabel overfaldevaliditet, og WHO-5, MDI og NDI vise fremragende indholdsvaliditet.

I studie II blev forekomsten af både spændingshovedpine og nakkesmerter i en klinisk gruppe af personer med migræne undersøgt. Denne gruppes fysiske aktivitetsniveau, trivsel, oplevet stress og selv-vurderede helbred blev undersøgt samt evnen til at deltage i fysisk aktivitet/træning i forhold til migræne, spændingshovedpine og nakkesmerter. Til sidst undersøgte vi, hvilken af de tre diagnoser føltes som mest belastende. Dette studie blev foretaget ved en spørgeskemaundersøgelse af 148 personer med migræne og 100 raske kontroller. Forekomsten af spændingshovedpine og nakkesmerter hos personer med migræne var på 67%; denne gruppe havde et lavt fysisk aktivitetsniveau, lavt trivselsniveau, højt niveau af oplevet stress og lavt selv-vurderet helbred i forhold til en rask befolkningsgruppe. Gruppen rapporterede en nedsat evne til at deltage i fysisk aktivitet på grund af deres migræne (høj grad), spændingshovedpine (moderat grad)

og nakkesmerter (lav grad). Den mest belastende diagnose var migræne efterfulgt af spændingshovedpine og nakkesmerter.

I studie III og IV blev effekten af et 12-ugers konditionstræningsprogram undersøgt med opfølgning efter seks måneder fra baseline hos personer med migræne, spændingshovedpine og nakkesmerter i et prospektivt, åbent, randomiseret, klinisk forsøg. Tooghalvtreds personer (26 i træningsgruppen og 26 i kontrolgruppen) gennemførte hele studieperioden. Træningsgruppen viste en signifikant forbedring af evnen til at deltage i dagligdagsaktiviteter, på grund af mindsket påvirkning af migræne, sammenlignet med kontrolgruppen. Der var en signifikant reduktion af frekvens, smerteintensitet og varighed af migræne i træningsgruppen i forhold til baseline, dog var der ingen forskel imellem grupperne (Studie III). I Studie IV blev effekten af konditionstræningsprogrammet undersøgt i forhold til smertefølsomhed. Der kunne ikke vises nogen effekt på muskelømhed eller på smertetærskler. Det konkluderedes at konditionstræning har en positiv effekt på en række migræne parametre og på migrænens indvirkning på dagligdagen, men denne effekt kan ikke forklares ud fra de anvendte test af muskelømhed og smertetærskler. Den positive effekt på migrænen kan muligvis forklares ved en adfærdsændring.

List of papers

1. Krøll LS, Hammarlund CS, Jensen RH and Gard G. Migraine co-existing Tension-Type Headache and Neck Pain: Validation of Questionnaires. Scandinavian Journal of Pain. *Scand J Pain* 2015; 8: 10-6.
2. Krøll LS, Hammarlund CS, Westergaard ML, Nielsen T, Sloth LB, Jensen RH and Gard G. Level of physical activity, well-being, stress and self-rated health in persons with migraine and co-existing tension-type headache and neck pain. *J Headache Pain* 2017; 18: 46.
3. Krøll LS, Hammarlund CS, Linde M, Gard G and Jensen RH. The effects of aerobic exercise for persons with migraine and co-existing tension-type headache and neck pain. A randomized, controlled, clinical trial. *Cephalalgia* 2018; 333102417752119 (Epub ahead of print).
4. Krøll LS, Hammarlund CS, Gard G, Jensen RH and Bendtsen L. Has aerobic exercise effect on pain perception in persons with migraine and co-existing tension-type headache and neck pain? A randomized, controlled, clinical trial. *Eur J Pain*, April 2018.

Abbreviations

AD-Index: Average Deviation Index
CI: Confidence Interval
ICHD-3 beta: International Classification of Headache Disorders 3rd edition beta version
I-CVI: Item-level Content Validity Index
Impact M-TTH-NP: Impact of Migraine Tension-Type Headache and Neck Pain
IPAQ: International Physical Activity Questionnaire
MDI: Major Depression Inventory
MSQ v. 2.1: Migraine Specific Quality of Life Questionnaire version 2.1
NDI: Neck Disability Index
NRS-11: 11-point Numeric Rating Scale
NP: Neck Pain
OR: Odds Ratio
QST: Quantitative Sensory Testing
RCT: Randomized Controlled Trial
RPE: Borg's scale of Rated Perceived Exertion
S-CVI/Ave: Scale-level Content Validity Index Average method
TTH: Tension-Type Headache
VO_2max: Maximum oxygen uptake
WHO-5: World Health Organization five-item Psychological Well-Being Index

General definitions

Physical activity

Physical activity (WHO-definition): *Any bodily movement produced by skeletal muscles that requires energy expenditure* (1).

Exercise (WHO-definition): *A subcategory of physical activity that is planned, structured, repetitive, and purposeful in the sense that the improvement or maintenance of one or more components of physical fitness is the objective* (1).

Aerobic exercise (WHO-definition): *Activity in which the body's large muscles move in a rhythmic manner for a sustained period of time. Aerobic activity – also called endurance activity – improves cardiorespiratory fitness. Examples include walking, running, and swimming, and bicycling* (1).

Pain terms

Pain threshold: *The minimum intensity of a stimulus that is perceived as painful* (2).

Allodynia: *Pain due to a stimulus that does not usually provoke pain* (2).

Hyperalgesia: *Increased pain from a stimulus that normally provokes pain. It reflects increased pain on supra-threshold stimulation* (2).

Temporal summation: Produced or increased pain generated by repeated stimuli (3).

Central sensitization: *Increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input* (2).

Thesis at a glance

Paper 1: *Migraine co-existing Tension-Type Headache and Neck Pain: Validation of Questionnaires*	
Aim	To investigate the validity of a newly developed questionnaire and five additional questionnaires all covering impact of migraine and co-existing tension-type headache and neck pain .
Methods	Face validity was conducted by group interviews of nine persons with migraine and co-existing tension-type headache and neck pain. Content validity was conducted by 13 headache experts who used rating schemes.
Results	The newly developed questionnaire showed acceptable face validity and excellent content validity. Acceptable face validity was found for four out of five additional questionnaires and excellent content validity was found for three out of five additional questionnaires.
Conclusion	The newly developed questionnaire in combination with the additional questionnaires may lead to a deeper understanding of the complexity of migraine with co-existing tension-type headache and neck pain, and may be useful in evaluation of treatment effects.
Paper 2: *Level of physical activity, well-being, stress and self-rated health in persons with migraine and co-existing tension-type headache and neck pain*	
Aim	To investigate the prevalence of co-existing tension-type headache and neck pain in a clinic-based sample of persons with migraine and their level of physical activity, well-being, stress and self-rated health compared to healthy controls.
Methods	Survey and headache and neck pain interview of 148 persons with migraine and 100 healthy controls.
Results	67% of persons with migraine suffered from co-existing tension-type headache and neck pain. They had lower level of physical activity and well-being, higher level of stress and poorer self-rated health compared to controls.
Conclusion	Migraine with co-existing tension-type headache and neck pain was highly prevalent. This group may require more individually tailored interventions to increase the level of physical activity, and to improve well-being and self-rated health.
Paper 3: *The effects of aerobic exercise for persons with migraine and co-existing tension-type headache and neck pain. A randomized, controlled, clinical trial.*	
Aim	To investigate the effects of aerobic exercise on migraine and co-existing tension-type headache and neck pain.
Methods	Randomized, controlled trial of 52 persons with migraine and co-existing tension-type headache and neck pain were randomized into exercise group or control group.
Results	26 persons in the exercise group and 26 in the control group completed the study. The exercise group showed a significant improvement in the ability to engage in daily activities compared to controls. Migraine frequency, pain intensity and duration were significantly reduced in the exercise group compared to baseline, although not significant compared to controls.
Conclusion	Aerobic exercise can be recommended as a supplement to medical treatment of migraine.
Paper 4: *Has aerobic exercise effect on pain perception in persons with migraine and co-existing tension-type headache and neck pain? A randomized, controlled, clinical trial.*	
Aim	To investigate the effect of aerobic exercise on pain perception for persons with migraine and co-existing tension-type headache and neck pain.
Methods	Randomized, controlled trial of 52 persons with migraine and co-existing tension-type headache and neck pain were randomized into exercise group or control group.
Results	26 persons in the exercise group and 26 in the control group completed the study. The exercise program did not show any effect on pericranial tenderness and pain thresholds.
Conclusion	Aerobic exercise showed no effect on pain perception.

Background

Prevalence

The prevalence of migraine in Europe is 15% (4). Persons with migraine often suffer from co-morbidities such as tension-type headache (TTH) and/or neck pain (NP). In previous population studies, co-existing TTH was reported in 94% of persons with migraine (5), and co-existing NP was reported in 89.3% of persons with migraine and co-existing TTH (6).

Definitions of migraine, TTH and NP

The International Classification of Headache Disorders (ICHD 3-beta)

Migraine without aura: Headache appearing in attacks with a duration of 4-72 hours, a moderate or severe pain intensity, pulsating quality, unilateral localisation, aggravated by physical activity, and associated with nausea and/or photophobia and phonophobia (7).

Migraine with aura: Aura appearing in attacks, lasting for minutes, of unilateral and fully reversible visual, sensory or other central nervous system symptoms that usually develop gradually and are usually followed by headache and associated migraine symptoms (7).

Chronic migraine: Headache occurring on 15 days or more per month for more than three months, which has the features of migraine on at least eight days per month (7).

TTH: Headache appearing in attacks with duration of 30 minutes to seven days, mild or moderate pain intensity, pressing quality, bilateral localisation, no aggravation by physical activity, no association with nausea but photophobia or phonophobia may be present (7).

Chronic TTH: Headache occurring on 15 days or more per month on average for more than three months (≥ 180 days per year), fulfilling the criteria for TTH but may be associated with photophobia, phonophobia or mild nausea (7).

The Neck Pain Task Force

NP: Pain located to the anatomic region of the neck with or without radiation to the head, trunk, and upper limbs. In the present studies NP concerns grade I-II out of IV (8). The anatomic region of the neck is shown in Figure 1.

Grade I: No signs or symptoms suggestive of major structural pathology and no or minor interference with activities of daily living.

Grade II: No signs or symptoms of major structural pathology, but major interference with activities of daily living.

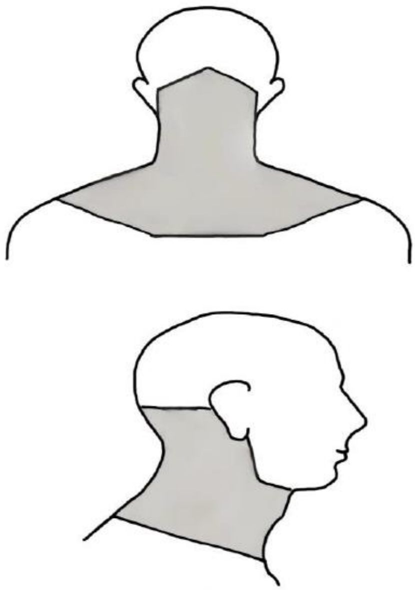


Figure 1
The neck region according to The Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders (8).

Headache diagnostics

At present, no exact diagnostic biomarkers exist to diagnose migraine or TTH. A headache diagnosis requires a clinical interview of headache history and headache characteristics together with a diagnostic headache diary and a neurological examination to exclude other neurological diseases.

To classify migraine and TTH, a semi-structured headache interview can be conducted, which has been found to result in a more accurate diagnosis of the headache compared to questionnaires (9). In addition, when the results of a telephone interview and a face-to-face interview were compared as a means to detect different subtypes of migraine no statistical differences were found (10).

A clinical interview may contain recall bias; therefore, a diagnostic headache diary can be used to reduce such bias. Based on an average rating during the day, a person with headache makes notes in the diary to assess headache duration, pain intensity, headache characteristics and medication intake for four weeks (11). Pain intensity is rated on an 11-point numeric rating scale with the end points 0 = no pain and 10 = worst imaginable pain. Jensen et al. (12) found that the combination of a diagnostic headache diary and a clinical headache interview significantly increased the adequacy of the headache diagnosis. Persons with headache found that a diagnostic diary was very easy to use and was also perceived as a useful tool by physicians in headache management (12) .

Non-pharmacological treatment

Lifestyle modifications such as exercise and avoiding or managing triggers together with relaxation and biofeedback are some of the recommended non-pharmacological strategies for persons with migraine and TTH (13-15). Persons with migraine and/or TTH who are difficult to treat may benefit from multidisciplinary treatment (16). The best outcome of multidisciplinary treatment of persons with these complex and multi-factorial headache disorders are those who adhere to pharmacological preventives, relaxation therapy, aerobic exercise and the suggested lifestyle changes (17).

Relaxation and biofeedback have been subjected to solid research for many years and have demonstrated a positive effect on headache frequency for both migraine and TTH (14, 18). In a recent systematic review and meta-analysis aerobic exercise has been reported to reduce migraine duration (19). Both physical activity and relaxation therapy have been suggested to increase the quality of life in persons with migraine (20, 21). Progressive muscle relaxation have been found to reduce migraine frequency (22) and a relaxation program has been shown to be effective in persons with headache and neck/shoulder pain (23).

Migraine and co-existing TTH and NP

Owing to clinical experience, a large part of persons with migraine seen in a specialized multidisciplinary headache clinic suffer from co-existing TTH and NP. This knowledge was confirmed by the population-based study by Ashina et al. (6). However, these combined conditions have not been adequately described in the literature, and knowledge about persons with migraine and co-existing TTH and NP is lacking.

The prognosis of migraine may deteriorate with co-existing TTH (24), and NP has been found to be a predictor of disability in persons with migraine (25).

Co-existing TTH in persons with migraine has been the subject of discussion (26-29). Some experts believe that migraine and co-existing TTH are two different conditions, but others believe that these conditions are not separate disorders.

NP is often described as an associated feature of the migraine attack itself (30, 31). Self-reported NP has been found to be associated with migraine and not with TTH in adolescents (32). Ashina et al. (6) reported that the odds ratio for NP in pure migraine was 2.5, in pure TTH the odds ratio for NP was 5.8 and for the combination of migraine and TTH the odds were 6.4. In an analysis of persons with migraine and co-existing TTH and NP, we found that NP associated with the migraine attack itself was reported by 54%, NP associated with TTH was reported by 94% and NP without headache was reported by 66% (33).

Impact

Migraine has a substantial impact on health-related quality of life (34). Reduced psychological well-being has been reported in persons with migraine in both a population-based study and a clinic-based study (35, 36) which may indicate stress or depression (37). Perceived stress has been associated with major depression in the general population (38). In general, persons suffering from migraine are very susceptible to stress which is a commonly reported migraine trigger and has also been reported as a TTH trigger (39, 40). Stress has been found to be increased in persons with migraine and migraine with co-existing TTH compared to headache-free individuals (41). However, the level of reported stress was higher in persons with pure migraine than those with the combination of migraine and TTH (41). The prevalence of poor self-rated health has been found to be higher in persons with migraine and co-existing recurrent headache compared to those with pure migraine and pure recurrent headache (42).

Some persons with headache and musculoskeletal pain change their behavioural patterns in order to manage pain. This strategy involves avoidance behaviour (43-45) and endurance strategies (45). Fear of pain has been found to predict headache severity, and persons with migraine have been shown to exhibit greater fear of pain than persons with TTH (43).

Pain

Migraine

Migraine is a well-defined brain disorder, but the cause of the disorder is not yet fully understood. Family history and environmental factors play a role in the occurrence of migraine (46). The relative risk for migraine without aura in first degree relatives of migraine probands has been estimated as 1.7-1.9 (47, 48); and for migraine with aura as 2.2-3.8 (47, 48). Also, early onset of migraine and severe pain intensity in migraine probands increase the risk of migraine in family members (48). Migraine has been shown to be more common among young adults and the male to female ratio is one to four (5).

Persons with migraine often report pain around the eye which corresponds to the upper division of the trigeminal nerve. Nociceptive inputs from afferent nerves from meninges and extracranial muscles, including muscles in the neck region, are transmitted to convergent neurons in the trigemino-cervical complex. These nociceptive inputs are then transmitted to the thalamus and on to the sensory cortex (49).

Central sensitization is an important phenomenon in the process towards chronicity and it is hypothesized that it can occur due to increased strong sensory inputs, mainly from myofascial tissues, leading to hypersensitivity of spinal cord neurons resulting in reduction of mechanical pain thresholds, which in turn can lead to hyperalgesia and allodynia (49).

Pain sensitivity

Pain and pain sensitivity are two different variables. Pain is the subjective personal experience expressed by the individual, while pain sensitivity can be measured directly by using quantitative sensory testing (QST) (3).

Pain perception has been found to be altered in persons with migraine presenting as allodynia and hyperalgesia (50). Both migraine and TTH have been associated with altered perception of electrical stimulation and pressure pain thresholds (51-53) and increased pericranial tenderness (54, 55). Increased pericranial tenderness has been found to a higher degree in persons with migraine and co-existing chronic TTH than in persons with chronic TTH alone (56).

NP is often reported as a migraine trigger (39), and generalized pressure pain hypersensitivity of the cervical muscles has been found in persons with migraine (57).

Musculoskeletal dysfunctions in the neck have been found in persons with headache. Watson and Drummond (58) were, thus, able to manually reproduce usual head pain between attacks from the upper cervical segments in both persons with migraine and with TTH. Also, Luedtke and May (59) were able to manually reproduce local NP and referred pain to the head in persons with migraine, and a significant correlation has been found between reported pain response from the upper cervical segments and migraine days per month. Florencio et al. (60) found altered muscle co-activation in persons with migraine who also reported neck and head pain during maximal isometric voluntary cervical contractions.

Therefore, both TTH and NP in persons with migraine may be contributing factors leading to allodynia and hyperalgesia.

The effects of exercise

Physical activity is a well-known physiotherapeutic treatment strategy which has a positive effect on health and well-being in healthy adults (61). Persons with migraine may avoid physical activity as they believe or have experienced that physical activity triggers their migraine attacks (39, 62, 63). However, low level of physical activity has been found to be associated with a higher prevalence of migraine (64) and an inverse relationship has been found between migraine and physical fitness (65). Aerobic exercise programs have shown positive effects on migraine frequency, migraine attack frequency, pain intensity and pain duration (20, 21, 66-69), and persons with TTH and NP have been reported to benefit from low load endurance craniocervical and cervicoscapular exercises (70). A summary of existing studies and reviews of the long term effect of aerobic exercise in migraine are listed in Table 1.

Aerobic exercise has been shown to decrease migraine pain intensity measured by subjective reporting of pain (20, 21, 66, 67, 71). However, both the acute and long term effect of aerobic exercise on pain perception in not clear. Studies have found divergent results both with regards to healthy subjects and different pain conditions.

Naugle et al. (72) have investigated healthy adults and found that moderate to vigorous physical activity performed for seven consecutive days was associated with less temporal summation of pain, and that self-reported vigorous physical activity, measured by IPAQ, exhibited greater conditioned pain modulation (73). In contrast, Jones et al. (74) did not show an effect of six weeks moderate to vigorous aerobic exercise on pressure pain thresholds, but found an improvement of ischemic pain tolerance in healthy adults.

Smith et al. (75) reported that the acute effect of 30 minutes of moderate aerobic exercise did not induce hypoalgesia in persons with chronic whiplash associated disorders measured by pressure pain thresholds. In contrast, Hooten et al. (76) showed an improvement of three weeks aerobic exercise on pain thresholds in persons with fibromyalgia. A longitudinal population study by Landmark et al. (75) found that persons performing moderate to high levels of exercise had less self-reported bodily pain over a period of 12 months.

Table 1
Studies and reviews after 2000 of the effect of aerobic exercise in persons with migraine.

Authors, year	Participants	Sex, age (completed the study)	Design	Intervention	Outcome measures	Results
Santiago et al. 2014 (69)	*N* = 60 Chronic migraine No previous exercise	26 women, 4 men. Mean 35 years exercise group, 31 years control group	Randomized comparative study	a. Amitriptyline alone b. Amitriptyline with 12 weeks aerobic exercise 40 minutes 3 times/week. One instruction by PT. Weekly assessment on telephone	Headache frequency, pain intensity, duration, medication use, BMI, Beck Depression and Anxiety Inventory	*Between group* Significant reduction in frequency, duration, pain intensity of chronic migraine; BMI, depression and anxiety in favour of exericise group
Darabaneanu et al. 2011 (66)	*N* = 30 Migraine minimum 2 attacks No previous exercise	13 women, 3 men. Mean 38 years exercise group, 34 control group	Pilot study Matched groups on age and gender– no randomiza-tion	No preventives a. supervisor exercise group 50 minutes aerobic exercise 3 times/week for 10 weeks b. Control group	Migraine frequency, pain intensity, duration, physical working capacity, depression, physical well-being, stress	*Within exercise group* Significant reduction in migraine days, pain intensity and duration, increase in working capacity and important part of the stress questionnaire
Varkey et al. 2011 (21)	*N* = 91 Migraine 2-8 attacks No previous exercise and relaxation	82 women, 9 men. Mean 44 years	RCT	No preventives Follow-up after 3 and 12 months a. Aerobic exercise 40 minutes 3/week 12 weeks (once a week with PT) b. Relaxation every day for 12 weeks (once a week with PT) c. topiramate for 12 weeks	Migraine attack, frequency, number of days, pain intensity, duration, acute medication, quality of life, aerobic capacity, level of physical activity	*Between groups* Significant reduction in pain intensity in topiramate group; increased aerobic capacity in exercise group. *Within group* Significant reduction of migraine attacks in all groups
Dittrich et al. 2008 (20)	*N* = 30 Migraine (no minimum of attacks)	30 women. Mean 34 years exercise group, 32 control group	RCT	Add on a. exercise group 6-week 45 minutes gymnastics and 15 minutes progressive muscle relaxation b. control group	Migraine pain intensity, attack frequency, Questionnaires of sensational and affective dimensions of pain, depression and quality of life	*Between groups* Significant reduction of pain intensity compared to controls. *Within exercise group* 87% reported aerobic exercise as helpful
Narin & Pinar 2003 (71)	*N* = 40 Selected persons with five attacks of migraine	40 women. Mean 35 years exercise group, 40 control group	Controlled trial alternately assigned	Add on Eight weeks intervention a. supervised exercise group one hour aerobic three times/week b. control group received medication	Migraine pain intensity, frequency and duration. Pain Disability Index, Quality of Life Scale and nitric oxide	*Between groups* Significant reduction of pain intenstiy compared to controls. *Within exercise group* Significant reduction in frequency and Pain Disability Index and nitric oxide

Köseoglu et al. 2003 (67)	*N* = 40 Migraine 2 attacks/month	34 women, 6 men. Mean 32 years	Single cohort, not controlled	No preventives aerobic exercise program, 40 minutes 3 times/week for 6 weeks. One instruction with physiotherapist. Weekly assessment on telephone.	Migraine attacks, pain intensity, duration and beta endorphin levels	*Within group* Significant reduction in attacks, pain intensity, duration and increase in endorphin levels

Authors	Design	Results	Future recommendations
Lüdtke et al. (19)	Systematic review and meta-analysis Physiotherapeutic interventions for headache and migraine	Reduction of migraine duration owing to aerobic exercise	Methodologically sound, randomized controlled trials with adequate sample sizes are required
Busch & Gaul (77)	Critical review Exercise as migraine treatment	Indication of a reduction of pain intensity in migraine owing to aerobic exercise	More studies based on evidence based medicine-criteria and RCT-studies are needed

Feasibility of physical activity

Varkey et al. (78) showed that an aerobic exercise program was feasible at a moderate intensity level three times a week for 12 weeks for persons with migraine. The program was well tolerated without aggravation of migraine. Experimental studies have shown that a migraine attack may be provoked by vigorous exercise in persons with migraine with/or without aura (79, 80). Thus, Hougaard et al. reported that four out of 12 participants (one migraine with aura and three with migraine without aura) developed migraine attack after a maximal exercise test (79); and in the test-retest study by Varkey et al. three out of 14 participants developed a migraine attack after both tests and five out of 14 participants developed a migraine attack after one of the tests (80). It is important to point out that most of these persons did not experience an attack afterwards even though they had reported physical activity to be a trigger factor for their migraine. Therefore, if no attacks are triggered after some attempts of performing vigorous or moderate physical activity advising persons with migraine to avoid physical activity may not be necessary. Physical activity has also been reported as a trigger factor for TTH (40, 63), but as far as is known; no similar experimental studies for either TTH or NP have been conducted.

Rationale

Based on clinical experience and the population-based study by Ashina et al. (6), we know that a large proportion of persons with migraine suffer from co-exiting TTH and NP. Knowledge about these combined conditions is sparse, and to our knowledge, no studies have described these persons' symptomatology, level of physical activity, psychological well-being, perceived stress or self-rated health. These characterizations are important when considering potential treatment strategies.

A review from 2008 of several studies on the effect of aerobic exercise on persons with migraine concluded that aerobic exercise may have a place in migraine therapy. However, the existing studies at that time generally did not meet the criteria for evidence-based medicine and recommended new and well-designed studies in this field (77). In the systematic review and meta-analysis from 2015 concluded that aerobic exercise showed a positive effect on migraine duration. However, like the review from 2008, this review also recommended new methodologically sound randomized controlled studies with adequate sample sizes (19).

To our knowledge, no previous studies have investigated the prevalence and impact of TTH and NP in a clinical sample of persons with migraine. As there is no single disease specific questionnaire covering these combined conditions a new questionnaire was required. There is increasing evidence of the positive effects of aerobic exercise on migraine. However, no previous studies have investigated the effect of aerobic exercise on the combined diagnoses of migraine, TTH and NP. The lack of studies investigating these aspects together with calls for new evidence of the effect of aerobic exercise has led to the aims of this thesis.

Aims

The overall aims of this thesis were to investigate the effects of an aerobic exercise program and the impact of migraine and co-existing TTH and NP in persons with these combined conditions.

Specific aims

- To develop and evaluate the Impact of Migraine, TTH and NP questionnaire (Impact M-TTH-NP), International Physical Activity Questionnaire (IPAQ short form), Migraine Specific Quality of Life Questionnaire (MSQ v. 2.1), Major Depression Inventory (MDI), World Health Organization 5-item Psychological Well-being Index (WHO-5) and Neck Disability Index (NDI) for face and content validity (Study I).
- To evaluate the prevalence of co-existing TTH and NP in a clinical sample of persons with migraine and to evaluate this group's level of physical activity, psychological well-being, perceived stress and self-rated health compared to healthy controls (Study II).
- To evaluate the effects of a three-month aerobic exercise program with regards to pain frequency, pain intensity, pain duration and the ability to engage in daily activities with follow-up six months from baseline (Study III).
- To evaluate the effects of aerobic exercise on pain perception regarding muscle tenderness and pain thresholds (Study IV).

In order to investigate the impact of migraine and co-existing TTH and NP and the effects of aerobic exercise three study designs were selected. Table 2 shows an overview of designs, participants, data collection and data analysis used in Studies I-IV.

Table 2
Overview of designs, participants, data collection, instruments and data analysis of Studies I-IV

	Study I	Study II	Study III	Study IV
Design	Psychometric	Cross-sectional	RCT	RCT
Participants	9 persons with migraine and co-existing TTH and NP, and 13 headache experts	148 persons with migraine 100 healthy controls	52 persons with migraine and co-existing TTH and NP	52 persons with migraine and co-existing TTH and NP (as in study III)
Data collection	Group interviews and rating schemes	Questionnaires	Headache diaries, fitness test and questionnaires	QST
Instruments	Headache and NP interview. Impact M-TTH-NP, IPAQ, MSQ v. 2.1, WHO-5, MDI and NDI	Headache and NP interview. Impact M-TTH-NP, IPAQ, WHO-5	Headache and NP interview. Diaries, ergometer bicycle, Impact M-TTH-NP, IPAQ, WHO-5	Headache and NP interview. Manual palpation, palpometer, algometer, keypoint workstation
Data analysis	I-CVI, S-CVI/Ave, AD-Index	Chi-square test, Mann-Whitney U-test, binary logistic regression	Independent samples T-test, Mann-Whitney U-test, paired-samples t-test, Wilcoxon signed-rank test	Mann-Whitney U-test, Wilcoxon signed-rank test

Methods

Participants

The inclusion criteria for all studies were age between 18-65 years including persons with migraine and co-existing TTH and NP for Study I; persons with migraine for Study II; and persons with minimum two attacks with migraine, one day with TTH and one day with NP per month for Studies III and IV.

The exclusion criteria for all four studies were whiplash injury, significant neck trauma (caused by trauma to the neck, fracture, distortion or violent attack that have caused the current NP), nerve root compression of the cervical spine, persistent headache attributed to traumatic injury to the head, medication overuse headache, cluster headache, trigeminal neuralgia, pregnancy, breastfeeding, severe physical and/or mental illness, abuse of alcohol and drugs, and inability to speak and understand Danish.

The exclusion criteria for headache-free and healthy controls in Study II were abuse of alcohol or drugs, inability to speak and understand Danish, regular intake of analgesics, NP and TTH frequency ≥ 1 day per month.

The participants were mainly recruited from a specialized headache centre in Denmark (Studies I-IV) and from advertisement (Studies III and IV). Headache-free and healthy controls (Study II) were recruited among hospital staff by modified snowball sampling and advertisement.

Assessment instruments used in the studies

Questionnaires

Impact of Migraine TTH and NP (Impact M-TTH-NP)

The multi-dimensional questionnaire Impact M-TTH-NP consists of 79 items covering pain, triggers, psychosocial, socioeconomic and work related aspects, based on a four-week recall period in most items. It is divided into six parts covering 1) sleep and stress, 2) migraine, 3) TTH, 4) NP, 5) extent of perceived degree of discomfort between migraine, TTH and NP and socio-economic consequences and

6) self-rated health, work ability (81) and physical activity. In most items an 11-point numeric rating scale (NRS-11) was applied with the end points 0 = no impact and 10 = most imaginable impact as applied in other studies (82, 83) (Appendix I).

Items used from Impact M-TTH-NP in Study II

Perceived stress

Perceived stress was assessed by a reliable and valid item from the QPS Nordic Questionnaire (84): *"Stress means the situation when a person feels tense, restless, nervous, or anxious, or is unable to sleep at night because his or her mind is troubled all the time. In the past four weeks, did you feel that kind of stress these days?"* Responses ranged from 0 (not at all) to 10 (very high degree). To be able to analyse the different levels of perceived stress, we coded scores 0-3 as low, scores 4-6 as moderate and 7-10 as high.

Self-rated health

Self-rated health was assessed by one item, originally derived from SF 36 (85): *"In general, how would you rate your current health?"* The response categories were: 1) very poor, 2) poor, 3) fair, 4) good or 5) very good. The variable was changed to a binary categorical variable "poor self-rated health" as applied in previous studies (6, 42). Scores 1-3 were coded as poor self-rated health.

The most burdensome condition of migraine, TTH and NP

Rating of the most burdensome condition was assessed by one item: *"In the past four weeks, to what extent does your migraine, TTH and NP generally affect you? If you consider all three conditions as adding up to 100%, to what extent does each of these conditions affect you?"*

Items used from Impact M-TTH-NP in Studies II and III

Ability to engage in daily activities

Perceived ability to perform daily activities was assessed by 15 items: *"In the past four weeks, when having migraine/TTH/NP, how much has your ability to perform the following activities been reduced?"*

Responses were rated on NRS-11 with the end points 0 = not reduced and 10 = reduced to a very high degree. The daily activities included were ability to perform household chores, perform paid work/study tasks, participate in social activities not including family activities, participate in family activities, and engage in physical activity e.g. aerobic exercise or strength training.

International Physical Activity Questionnaire short form (IPAQ)

IPAQ short form (86) consists of 7 items concerning time spent on low, moderate and vigorous physical activity during the last 7 days measured in hours and minutes. Participants were classified as having low, moderate or high levels of physical activity based on the standard algorithm (87). The IPAQ protocol considers performed physical activity and their corresponding metabolic equivalent task (MET). One MET is equivalent to energy expenditure while resting. Participants were excluded from the analyses if they answered “don’t know/uncertain” in any of the categories of walking, moderate or vigorous physical activity, and if time spent on any of the categories were unreasonably high (87).

Migraine-Specific Quality of Life Questionnaire (MSQ v. 2.1)

MSQ v. 2.1 is a 14-item condition specific quality of life questionnaire for persons with migraine based on a 4-week recall period (88). It consists of three dimensions; role restrictive (seven items) that measures normal activities limited by migraine, role preventive (four items) that measures normal activities interrupted by migraine, and emotional functions (three items) that measures the emotional effects of migraine. Responses are rated on 6-point Likert categories with the end points 1 = none of the time and 6 = all of the time. Raw scores are transformed to a 0 – 100 scale. Higher score indicate higher quality of life.

World Health Organization 5-item Psychological Well-Being Index (WHO-5)

WHO-5 assesses psychological well-being by five positively worded items based on a two-week recall period (89). Responses were rated on six-point Likert categories with the end-points 0 = at no time and 5 = all of the time. The scores were summated (maximum score 25) and then multiplied by 4 (range 0 to 100 with lower scores indicating lower well-being). The cut-off level of ≤ 50 was used to indicate poor psychological well-being, which may indicate stress or depression (37). In addition, WHO-5 has a high sensitivity and specificity as a screening instrument for depression (37).

Major Depression Inventory (MDI)

MDI can be used as a diagnostic instrument for depression and as a depression rating scale (90). The questionnaire consists of 12 items based on a two-week recall period. Item number 8 and 10 has alternatives a or b, and the highest score is selected. Responses are rated on six-point Likert categories with the end-points 0 = at no time and 5 = all of the time (91). Scores 20-24 indicate mild depression, scores 25-39 indicate moderate depression, and scores 30 or more indicate severe depression on the depression rating scale.

Neck Disability Index (NDI)

NDI assesses the current degree of disability caused by NP (92). The questionnaire consists of ten items, and is scored on 6-point Likert categories from no disability to highest degree of disability (92). The maximum sum score is 50. Higher score indicate higher disability.

Quantitative Sensory Testing (QST)

The selected tests aimed to test for pericranial tenderness and pain thresholds, supra-thresholds and temporal summation. Pain thresholds were measured both locally and peripherally. The participants were not allowed to take acute medication on the day of testing, and they were tested on a migraine free day. All tests were conducted by a specially trained and experienced physiotherapist (LSK) and an experienced technician (HA). None of the testers were blinded to the participants grouping.

Total Tenderness Score and Local Tenderness Score

The recording of pericranial tenderness was performed on eight pairs of muscles and tendon insertions (masseter, temporal, frontal, sternocleidomastoid and trapezius muscles and muscle insertions onto the occiput; the coronoid and mastoid processes) (Figure 2). The test was performed according to the total tenderness scoring system as described by Bendtsen et al. (93) by applying manual rotating palpation at each location bilaterally, and the degree of tenderness was rated on a 4-point scale according participant’s response (0 = denial of tenderness, no visible reaction, 3 = verbal report of marked pain and visible expression of discomfort). The scores were summated with a maximum score of 48.

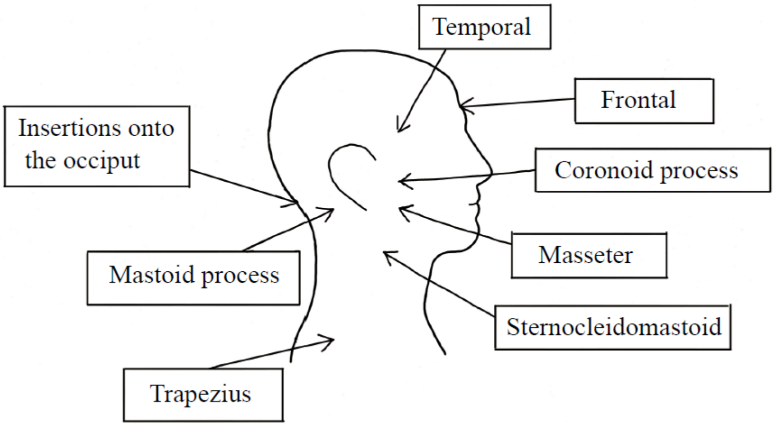


Figure 2
Palpation points on eight pairs of muscles and tendon insertions (masseter, temporal, frontal, sternocleidomastoid and trapezius muscles and muscle insertions onto the occiput; the coronoid and mastoid processes).

Local tenderness score was measured on a predefined point over the splenius capitis muscle (three cm cranial to the processus spinosus of C7 (prominent vertebra) and approximately two cm lateral to the midline). The pressure was applied with small rotating movements sustained for 4-5 seconds. The degree of tenderness was scored on a 0-100 mm VAS-scale after a pre-specified pressure of 160 arbitrary units using a constructed palpometer to standardise the pressure of the tester (94).

Pressure Pain Threshold

Pressure pain threshold and supra-threshold pressure pain sensitivity were recorded on three predefined points; over the splenius capitis muscle, on the temporal muscle (2 cm behind the lateral orbital margin and 2 cm above the orbito-temporal line) and on the dorsum of the second finger (middle phalanx). The test was conducted with an algometer type II, (Somedic, AB, Stockholm, Sweden) with a circular stimulation probe (0.5 cm^2) and a pressure-loading rate of 10 kPa/s (95). The pressure pain threshold was defined as when the feeling of pressure changes to the feeling of pressure and pain. Pressure pain threshold were recorded three times and a mean score was calculated. The supra-threshold pressure pain sensitivity was measured by the mean score of the pressure pain threshold and multiplied by 1.5. Supra-threshold pressure pain sensitivity was measured three times scored on a 0-100 mm VAS-scale and a mean score was calculated.

Sensitivity to electrical stimulation and temporal summation

The electrical pain thresholds were recorded on a predefined point in the splenius capitis muscle and in the anterior tibial muscle (one-third of the distance from the apex patellae to the lateral malleolus) by needle electrodes (30G, Alpine Biomed ApS, Denmark) on a Keypoint Workstation, (Alpine Biomed Corp, USA). The strength of the electrical stimulus was gradually increased with notion of value in mA of 1 ms duration. The electrical pain threshold was defined as the weakest stimulus perceived as painful. Electrical pain thresholds were recorded three times and a mean score was calculated. The supra-threshold single electrical pain stimulus pain score was measured by applying a single electrical stimulus multiplied by 1.5 the electrical pain threshold and measured three times. The degree of supra-threshold electrical pain sensitivity was scored on a 0-100 mm VAS-scale. Temporal summation was applied by inducing a train of five 1-ms pulses at 2 Hz with an intensity of 1.5 times the electrical pain threshold and measured three times. The fifth stimulus in the train was scored on the 0-100 mm VAS-scale. These methods have been applied in earlier studies (96, 97).

Assessment of physical fitness and rated perceived exertion

Test of physical fitness

The Åstrand's submaximal bicycle test (98, 99) was applied to estimate maximum oxygen uptake (VO_2max). The test was performed on an ergometer bicycle (Monark Ergomedic 939E PC, Monark Exercise AB, Stockholm, Sweden). The pulse rate was monitored by a Polar pulse belt (ProTerapi A/S, Brøndby, Denmark) during the test. The participants biked for six minutes; within the first three minutes the load was adjusted in order to get the pulse rate to exceed 120 beats per minute. This test was conducted by a specially trained and experienced physiotherapist (LSK) and an experienced technician (HA). None of the testers were blinded to the participants grouping.

Borg's scale of Rated Perceived Exertion (RPE scale)

A modified version of the Borg's RPE scale (100) was applied. Borg's RPE scale is a subjective rating tool to monitor the perceived feelings of effort experienced during endurance activity. It is measured on a 15-point scale (6-20) with the end points 6 = no exertion at all, and equals to resting heart rate, 20 = maximal exertion. As some of the participants were using beta-blocker as migraine preventive medication, this tool was applied in order to avoid monitoring the pulse rate. The perceived intensity of effort during endurance activity was monitored by the perceived breathing rate corresponding to the RPE scale (101). Table 3 shows the relative intensity of effort assessed by the degree of perceived degree of breathing when exercising.

Table 3
The relative intensity of effort assessed by the degree of breathing when exercising and the corresponding Borg's scale of Rated Perceived Exertion (RPE scale).

RPE Borg's scale	Own perception of breathing
<10	Not out of breath
10-11	Lightly out of breath conversation fluent
12-13	Slightly out of breath conversation possible
14-16	Out of breath conversation in short sentences
17-19	Very out of breath – words not sentences
20	Hyperventilate

Headache assessment and diaries

Headache interview

A modified semi-structured headache interview contains questions about headache symptomatology (9, 10). It is subdivided into questions about migraine with or without aura, TTH and supplemented with questions regarding NP symptomatology. In contrast to the diary, the interview allows the interviewer to reword questions to clarify uncertainties. Further, the interview contains questions about duration of disease and the number of attacks of migraine and aura since onset.

Diagnostic headache diary

The diagnostic headache diary (11) contains information about headache characteristics from which migraine or TTH were classified according to the definitions of the ICHD-3 beta (7). The headache diary was supplemented with questions about NP and with a drawing of the neck region to assure that the participants rated their NP in the same distribution area. Frequency, duration and pain intensity of migraine, TTH and NP and medication intake were assessed from 4-week diary recordings.

Exercise diary

The participants were provided with an exercise diary in order to monitor and keep records of their exercise frequency, type of exercise, their degree of motivation, headache and NP before and after exercising and to report possible side effects caused by the exercise program.

Procedures

All participants fulfilling the criteria and accepting participation in Studies I-IV, except from headache experts in Study I and healthy controls in Study II, were interviewed using the modified semi-structured headache interview (9, 10) and have been examined by neurologist (Studies I-IV) and physiotherapist (Studies I, III and IV).

Development and validation of questionnaires assessing the impact of migraine and co-existing TTH and NP (Study I)

To investigate the impact of migraine and co-existing TTH and NP a wide range of questionnaires were selected to cover this topic adequately. First, the multi-dimensional questionnaire Impact M-TTH-NP was developed.

The Impact M-TTH-NP questionnaire was a revised version of two questionnaires used in an earlier population-based study by Lyngberg et al. (5). Clinically relevant items were selected based on what may possibly be changed by an aerobic exercise program. Therefore, items like food habits and work equipment were left out. Many of the original items had binary response categories which was then changed into NRS-11 (end points, 0 = no impact and 10 = most imaginable impact) to make them more sensitive for possible changes and because this rating scale has been used in earlier studies (82, 83). Some items were gathered together in tables to make them faster to reply. Additional items were added regarding sleep, stress, physical activity and workability. Possible modifiable triggers were selected, and an item was added asking about the most burdensome condition of the three conditions, migraine, TTH and NP. Many of the items were repeated for migraine, for TTH and for NP (Appendix I).

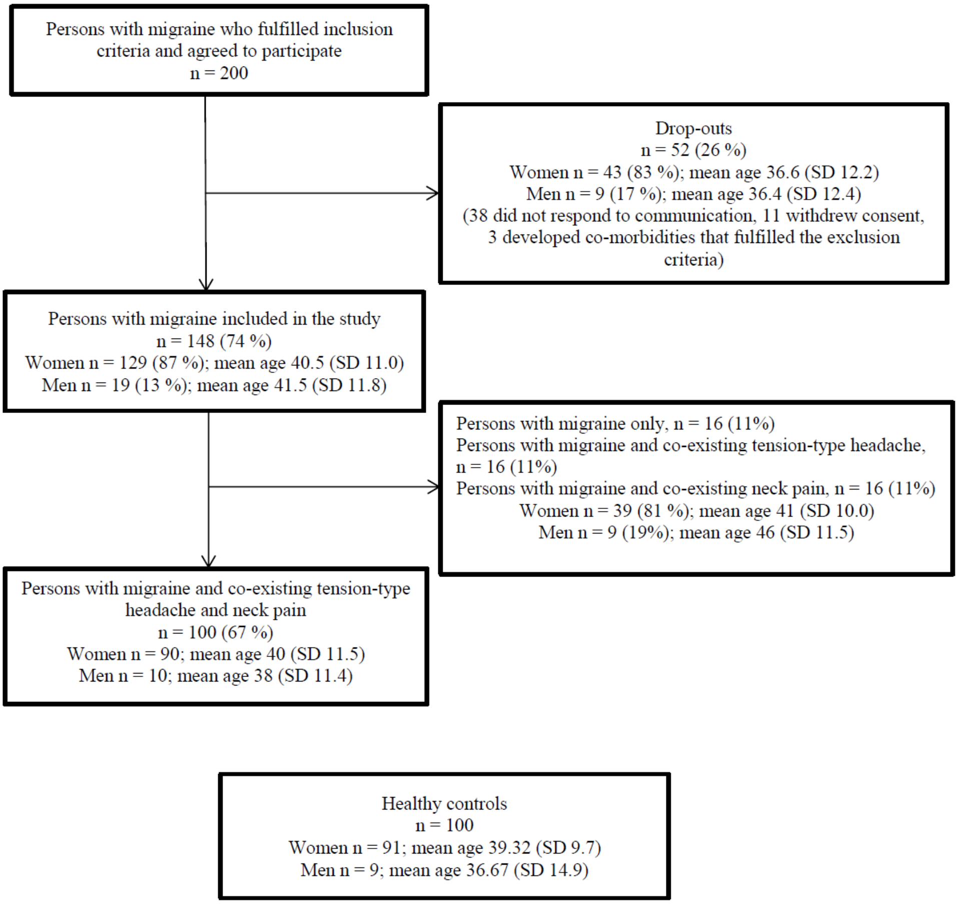
Additional five questionnaires were selected in order to cover most aspects of "impact", thus, we chose to add IPAQ to cover the level of physical activity, MSQ to cover condition specific quality of life, WHO-5 to cover psychological well-being, MDI to cover depression, and NDI to cover condition specific disability of NP.

To understand whether the selected questionnaires covered the impact of migraine and co-existing TTH and NP we recruited 14 persons with these combined conditions between September 2012 and March 2013 (five declined participation, two due to time constraint, one due to illness and two did not state any explanation); and 13 headache experts between August 2012 and October 2012 to evaluate face and content validity, respectively.

The evaluation of face validity by persons with migraine and co-existing TTH and NP were done by group interviews which lasted for 1- 1½ hours. Persons with migraine and co-existing TTH and NP (in the following called group-participants) were introduced to the background, purpose and procedure of the group interview and the questionnaires were reviewed for clarity, understanding, relevance and meaningfulness. The evaluation of content validity by headache experts was done by rating schemes. The experts also received information about the background and purpose of the study and detailed instructions. Each item was rated using four-point Likert categories 1 = not relevant and 4 = highly relevant (102) and to provide written comments on perceived relevance/irrelevance, ambiguity, wording and whether additional items were needed.

Prevalence and impact of migraine and co-existing TTH and NP (Study II)

A clinical sample of 200 persons with migraine were recruited between February 2014 and March 2015. Between June 2014 and October 2015, 100 headache-free and healthy controls were recruited. Healthy controls were matched to the included persons with migraine by the mean value of age and the percentage distribution of sex. All participants were provided with the questionnaires evaluated in Study I. Of the 200 persons with migraine, 148 (74%) returned the questionnaires and were included in the study (Figure 3).



Figur 3
Flow chart of the inclusion procedure of a clinic-based sample of persons with migraine, Study II.

Effects of aerobic exercise on migraine and co-existing TTH and NP (Studies III and IV)

Seventy persons were recruited between January 2013 and July 2015 and were randomized into an exercise group or control group. The block randomization sequence was conducted by an independent medical doctor and based on a computer generated list with a block size of six. The results of the randomization were sealed in envelopes provided with consecutive numbers by an independent physiotherapist. The enrolling physiotherapist (LSK) was not involved in this procedure. A total of 18 participants discontinued from the study after inclusion (Figure 4).

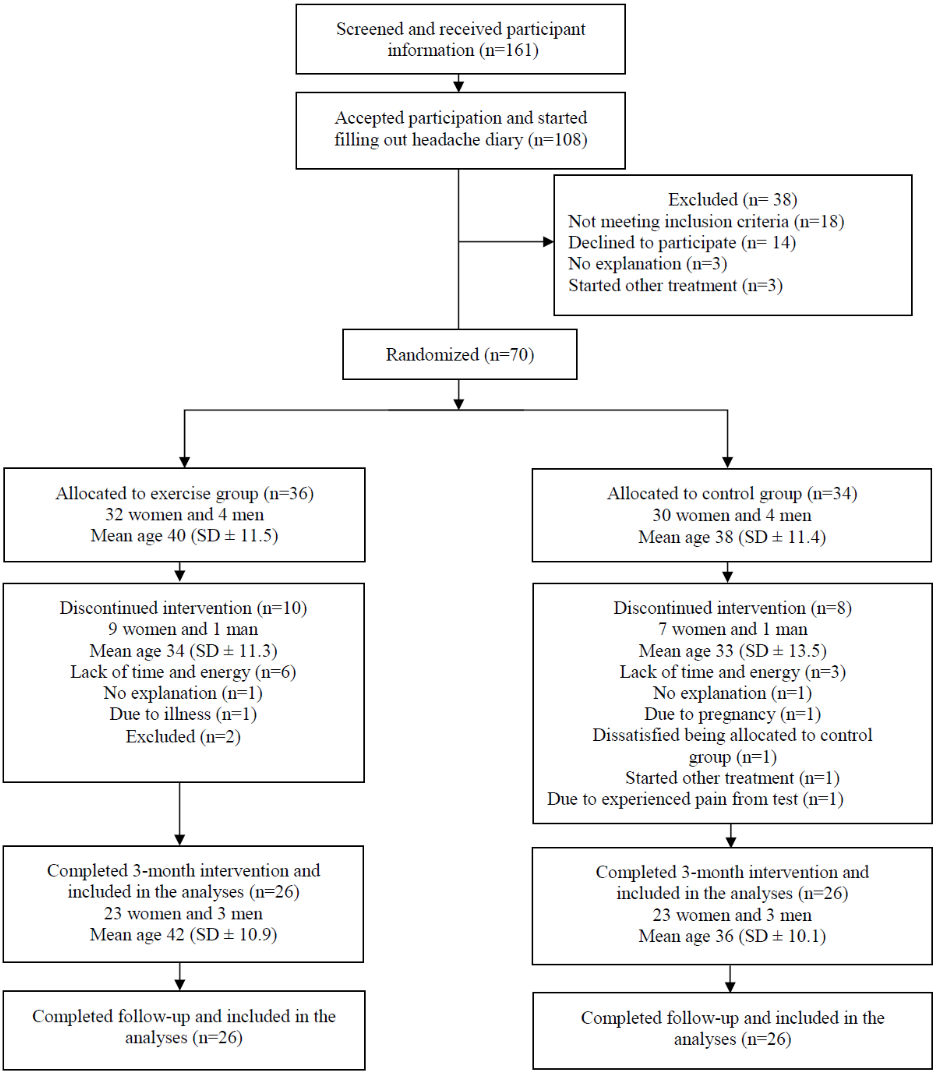


Figure 4
Flow chat of the study procedure, Studies III and IV.

Before entering the study the participants had filled out a four-week diagnostic headache and NP diary which served as baseline. The diary was also filled out daily for the first three months of the study period and again four weeks before the end of follow-up (Figure 5).

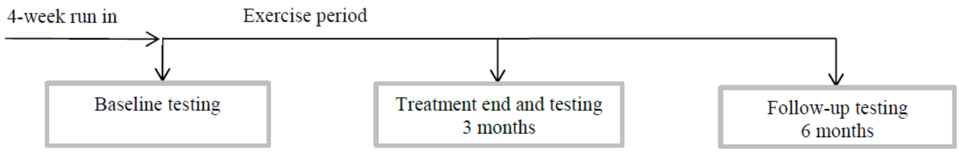


Figure 5
Timeline of testing and treatment, Studies III and IV.

Exercise group. Participants in the exercise group trained three times a week for three months. Once a week they trained with a physiotherapist (LSK) and twice a week at home or at a gym. They were instructed to exercise minimum once a week on a bike (indoor or outdoor) and minimum once a week on a cross-trainer or brisk walking. Those who were comfortable with running could choose to do that as an alternative to cross-training or brisk walking. Each training session lasted for 45 minutes and exercise intensity was monitored by the individual's perceived breathing rate corresponding to the modified RPE (100). The exercise period was divided into ten minutes warm-up (slightly out of breath but conversation is possible; corresponding to 11-13 RPE), 30 minutes endurance activity (out of breath; conversation in short sentences; corresponding to 14-16 RPE) and five minutes cool-down (slightly out of breath but conversation is possible; corresponding to 11-13 RPE). During exercise lessons (with LSK), the breathing rate was monitored by letting the participants read a short text aloud.

During the treatment period, participants filled out an exercise diary with information on date and form of exercise. Also, participants were encouraged to write down perceived side effects caused by exercising. They were allowed to miss a maximum of five lessons out of 36. The treatment period was followed by a post-treatment period where participants could continue to exercise according to their own preference.

Control group. Participants in the control group were instructed to carry on with their daily life as usual. Every four weeks, they received an email asking them to submit the headache and NP diary. After follow-up they were offered individually tailored physiotherapy. This information was written in the participant information and repeated at the first visit with the physiotherapist (LSK).

During the study period, all participants continued with prescribed preventive and acute medication (adjusted regularly when needed). Those who were already engaged in some form of exercise activity were allowed to continue as before. They were not allowed to seek other nonpharmacological treatment (such as acupuncture or psychological therapy) for their headache and NP during the study period.

Statistics

The statistical analyses were performed using IBM SPSS version 19 and 22. Statistical significance was assumed when $p < 0.05$.

Development and validations of questionnaires assessing the impact of migraine and co-existing TTH and NP (Study I)

To quantify experts' ratings the responses were dichotomized into not relevant (rating 1 or 2) and relevant (rating 3 or 4). I-CVI was the proportion of experts giving a rating of 3 or 4 (103). I-CVI ≥ 0.78 was considered as having excellent content validity (104).

S-CVI/Ave was used as an average calculation across the I-CVI for each item in order to assess the degree of relevance of the entire questionnaire. S-CVI/Ave ≥ 0.90 was considered as having excellent content validity (104).

The AD index for Likert-type scales was used to measure interrater agreement (105). The AD index measures the dispersion of responses about the median. This was calculated as the sum of differences from the median in absolute values divided by the number of experts. At 5% level of significance the cut-off limit was 0.65 for 13 raters. Values < 0.65 indicated acceptable and statistically significant agreement (105).

Prevalence and impact of migraine and co-existing TTH and NP (Study II)

The prevalence of TTH and NP in persons with migraine and their clinical characteristics were presented with descriptive statistics. Chi-square test was used to test for differences in sex, educational attainment, physical activity, psychological well-being, stress and self-rated health between persons with migraine and co-existing TTH and NP and healthy controls.

Independent-samples t-test was used to test for differences in age as age was tested as normally distributed by the Shapiro-Wilk test. Separate binary logistic regressions were performed with migraine and co-existing TTH and NP as the outcome variable and the following as covariates: Physical activity (low, moderate and high), psychological well-being (score ≤ 50, yes or no), perceived stress (low, moderate and high), and poor self-rated health (yes or no). These analyses were controlled for educational attainment. Results from the logistic regression were presented as odds ratios (OR) with 95% confidence intervals (CI).

Applied questionnaires were Impact M-TTH-NP (selected items were perceived stress, self-rated health, the most burdensome condition of migraine, TTH and NP, the ability to engage in physical activity owing to migraine, TTH and NP), IPAQ and WHO-5.

Responses to IPAQ that were unreasonably high were treated as measurement errors and excluded from the analyses of levels of physical activity.

Effects of aerobic exercise on migraine and co-existing TTH and NP (Study III)

Thirty participants were needed to detect a clinically relevant difference in migraine days of 30% with a power of 80% (106). To take drop-outs into account 10 participants were added.

Clinical characteristics of participants were presented descriptively as counts, percentages, or means and standard deviations.

Independent-samples t-test was used to analyse between-group differences from baseline to the end of the treatment period, and from baseline to the end of follow-up. If data were not normally distributed according to the Shapiro-Wilk test, they were transformed into natural logarithms. Transformed data were used to calculate two-tailed *p*-values and confidence intervals (CI). Analyses were done per protocol.

Wilcoxon signed-rank test or the dependent samples t-test were used to analyse within-group changes (depending on whether data were normally distributed according to the Shapiro-Wilk test) from baseline to the end of the treatment period, and from baseline to the end of follow-up.

Applied questionnaires were Impact M-TTH-NP (selected items of the ability to engage in daily activities owing to migraine, TTH and NP), IPAQ and WHO-5.

Responses to IPAQ that were clearly outside the maximum range of physical activity were treated as measurement errors and excluded from the analyses of MET-minutes/week.

Participants who received beta blockers were excluded from the Åstrand's submaximal bicycle test.

Post hoc analyses were subsequently performed for changes between exercise and control groups from baseline to the end of the treatment period, and from baseline to the end of follow-up with regards to days with migraine for those with chronic migraine and for those without chronic migraine and co-existing TTH (in the following called episodic migraine) in order to investigate whether these two groups may show different effects.

Primary endpoint. Change in number of days with migraine

Secondary endpoints. Changes in (1) number of days with TTH and NP, (2) pain intensity, (3) pain duration, (4) area under the curve (AUC) of duration x pain intensity for migraine, TTH and NP, (5) physical fitness, (6) level of physical activity, (7) psychological well-being, and (8) perceived ability to perform daily activities.

Effects of aerobic exercise on pain perception (Study IV)

Mann-Whitney U-test was used to analyse between-group differences from baseline to the end of the treatment period, and from baseline to the end of follow-up. Analyses were done per protocol. Wilcoxon signed-rank test was used to analyse within-group changes from baseline to the end of the treatment period, and from baseline to the end of follow-up.

To further analyse pain perception, post hoc analyses were subsequently decided. The analyses were done on responders from Study III. Responders were defined as persons in the exercise group that showed decreased number of days with migraine by more than 30% during the last four weeks of exercise (n = 13). Also, post hoc analyses were performed for changes between exercise and control groups for those with chronic migraine and for those with episodic migraine, respectively, with regards to the primary endpoint.

Primary endpoint. Change in total tenderness score.

Secondary endpoints. Changes in local tenderness score, pressure pain thresholds, pain rating of supra-threshold pressure pain, electrical pain threshold, pain rating of electrical pain supra-threshold and temporal summation

Ethical considerations

All participants received oral and written information, and all signed an informed consent form. Personal data were deleted in accordance to the requirements of the Danish Data Protection Agency. The local ethical committee of the Capital Region of Denmark approved the studies of this thesis, protocol no H-1-2011-090. The studies were conducted in accordance with the Declaration of Helsinki. Study III and IV were registered in the Protocol Registration and Results System; Register Number: NCT02269501.

Results

Development and validation of questionnaires assessing impact of migraine and co-existing TTH and NP (Study I)

Face validity. The nine group-participants were women, mean age 38 (range, 28-50) years. Four were employed, three on sick leave, one unemployed and one was a student. They had an average headache history of 17 (range, 6-24) years and an average frequency of 22 days per month with migraine and co-existing TTH and an average NP frequency of 23 days per month. The face validation of the Impact M-TTH-NP questionnaire ascertained that no items needed to be removed. One item concerning the total amount of sleep at night was added to the questionnaire. In addition, 12 items needed revision and were rephrased. The item concerning cost of health care consultations was rephrased, and the recall period was changed from a four-week recall to a three-month recall period, as the likelihood of capturing various health care consultations was higher with the latter. All revised items were perceived as relevant and meaningful by most group-participants. Some of them would have liked to have had the opportunity to describe their ability to perform daily tasks despite headache and NP.

Content validity. The 13 headache experts were nine medical doctors, two physiotherapists, one headache nurse and one psychologist (eight women and five men), mean age 42 (range, 27-71) years. They had worked with headache diseases for an average of 9 (range, 2-38) years, and had research experience for an average of 8 (range, 1-40) years. Evaluation of content validity of the Impact M-TTH-NP questionnaire showed that 72/78 (92 %) of the items obtained excellent content validity, and 71/78 (91%) obtained AD index below 0.65. In all, 9/78 items did not meet either the limit for excellent I-CVI and/or acceptable AD index. These nine items represented sleep quality, difficulty falling asleep, lack of rest and work at a moderate intensity as triggers for migraine, work at moderate intensity as a trigger for NP, reduced productivity at work measured in hours, current and future job, and physical activity. The S-CVI/Ave for the entire Impact M-TTH-NP questionnaire showed excellent content validity (Table 4).

Table 4

Content validity of Impact of Migraine, Tension-Type Headache and Neck Pain questionnaire (Impact M-TTH-NP) using item-level content validity index (I-CVI), Average Deviation (AD) index as a measure of interrater agreement, and scale-level content validity index average method (S-CVI/Ave), Study I.

Impact M-TTH-NP Part 1 - 6	**I-CVI ≥ 0.78[a] (number of items)**	**AD index < 0.65[b] (number of items)**	**S-CVI/Ave[c]**
Part 1. Sleep and stress (*n* = 5 items)	3	4	0.89
Part 2. M (*n* = 21 items)	21	19	0.93
Part 3. TTH (*n* = 20 items)	20	20	0.94
Part 4. NP (n = 20 items)	20	19	0.94
Part 5. Perceived degree of discomfort between M, TTH, and NP, and socio-economic consequenses (*n* = 6 items)	5	5	0.90
Part 6. Self-rated health, work ability & physical activity (*n* = 6 items)	3	4	0.77

[a] I-CVI the cut-off limit for excellent content validity = 0.78.
[b] AD index < 0.65 = interrater agreement.
[c] S-CVI/Ave the cuff-off limit for excellent content validity = 0.90.

IPAQ, calculating the activity into minutes was perceived as difficult and not meaningful by some group-participants. Experts also had critical comments about this questionnaire e.g. one expert wrote, “The activities are too difficult to remember”. Excellent I-CVI was found in 5/7 items, AD index < 65 in 5/7, S-CVI/Ave not meeting the criteria for excellent content validity (Table 5).

Most group-participants perceived the MSQ v. 2.1 as relevant, whereas some experts reported that this questionnaire was redundant as most of the items were covered by the Impact M-TTH-NP questionnaire. Excellent I-CVI was found in 9/14 items, AD index < 65 in 8/14, S-CVI/Ave not meeting the criteria for excellent content validity (Table 5).

WHO-5 was perceived as relevant and meaningful by group-participants. One expert wrote, “Very general questions; which conclusions may be drawn from them?” Excellent I-CVI was found in 5/5 items, AD index < 65 in 4/5, excellent S-CVI/Ave (Table 5).

MDI was perceived as relevant and meaningful by group-participants. One expert wrote, “Important to screen for depression, but many questions are repeated in the other questionnaires”. Excellent I-CVI was found in 12/12 items, AD index < 65 in 12/12, excellent S-CVI/Ave (Table 5).

NDI was perceived as relevant, although, the items concerning personal care and lifting were considered difficult to answer by some group-participants. The response categories were considered too vague and open for interpretation by one expert. Excellent I-CVI was found in 8/10 items, AD index < 65 in 10/10, excellent S-CVI/Ave (Table 5).

Table 5
Content validity of five additional questionnaires using item-level content validity index (I-CVI), Average Deviation (AD) index as a measure of interrater agreement, and scale-level content validity index average method (S-CVI/Ave), Study I.

Questionnaire	I-CVI ≥ 0.78[a] (number of items)	AD index < 0.65[b] (number of items)	S-CVI/Ave[c]
IPAQ short form[d] Items n = 7	5	5	0.87
MSQ v. 2.1[e] Items n = 14	9	8	0.84
WHO-5[f] Items n = 5	5	4	0.94
MDI[g] Items n = 12	12	12	0.95
NDI[h] Items n = 10	8	10	0.92

[a] I-CVI the cut-off limit for excellent content validity = 0.78.
[b] AD index < 0.65 = interrater agreement.
[c] S-CVI/Ave the cuff-off limit for excellent content validity = 0.90.
[d] International Physical Activity Questionnaire.
[e] Migraine-Specific Quality of Life Questionnaire.
[f] World Health Organization five-item Psychological Well-Being Index.
[g] Major Depression Inventory.
[h] Neck Disability Index.

Prevalence and impact of migraine and co-existing TTH and NP (Study II)

The prevalence of co-existing TTH and NP in a clinical sample of persons with migraine was 67% (n = 148); 11% suffered from migraine only (n = 16), 11% suffered from migraine and co-existing TTH (n = 16), and 11% had migraine and co-existing NP (n = 16).

Persons with migraine and co-existing TTH and NP were significantly less physically active, reported significantly lower psychological well-being, had higher levels of perceived stress and poorer self-rated health compared to healthy controls (Table 6).

Tabel 6
Clinical charcteristics and health-related variables of persons with migraine and healthy controls, Study II.

	All *N* **= 148**	**M-TTH-NP** *N* **= 100**	**Healthy Controls** *N* **= 100**	***p*-value M-TTH-NP healthy controls**
Age, mean (SD)	41 (11.1)	40 (11.4)	39 (10.2)	0.49
Sex, n (%)				0.81
Women	129 (87)	90	91	
Men	19 (13)	10	9	
Educational attainment, n (%)				0.014
< 3 years higher education	57 (40)	42	26	
≥ 3 years higher education	85 (60)	56	73	
Missing, n	6	2	1	
Physical activity[a], n (%)				0.001
Low	29 (23)	18 (21)	7 (8)	
Moderate	50 (40)	34 (41)	25 (27)	
High	47 (37)	32 (38)	59 (65)	
Missing, n	22	16	9	
Psychological well-being ≤ 50[b], n (%)				< 0.001
No	75 (51)	48	89	
Yes	73 (49)	52	11	
Missing, n	1	1		
Stress[c], n (%)				< 0.001
Low	61 (42)	38	66	
Moderate	33 (22)	22	21	
High	53 (36)	39	13	
Missing, n	1	1		
Poor self-rated health[d]				< 0.001
No	58 (39)	38	96	
Yes	90 (61)	62	4	
Migraine days/month, median (q1, q3)	6 (4, 10)	6 (3, 10)	-	-
TTH days/month, median (q1, q3)	9 (4, 18)	9 (4, 15)	-	-
NP days/month, median (q1, q3)	11.5 (5, 30)	13 (5, 30)	-	-
Chronic migraine, n (%)	41 (28)	28	-	-
Chronic TTH, n (%)	21 (14)	17	-	-
Chronic NP, n (%)	54 (37)	49	-	-

M = migraine, NP = neck pain, *N* = numbers, q = quartiles, q1 and q3 refer to first and third quartiles, SD = standard deviation, TTH = tension-type headache.
[a]Assessed using the International Physical Activity Questionnaire (IPAQ short form) low, moderate and high physical activity was based on time and energy expenditure in the past 7 days.
[b]Assessed using the World Health Organization five-item Well-Being Index (WHO-5) sum score from 0-100; sores ≤ 50 indicate poor psychological well-being.
[c]Assessed using stress scores with end-points 0 = no stress at all and 10 = very high degree of stress; scores 0-3 = low, scores 4-6 = moderate, scores 7-10 = high stress.
[d]Assessed using self-rated health with end-points 1 = very poor to 5 = very good; scores 1-3 indicated poor self-rated health.
Independent-samples t-test was used to test for differences in age; Chi-square test was used to test for difference in sex, educational attainment, physical activity, psychological well-being, stress and poor self-rated health.

Migraine and co-existing TTH and NP were strongly associated with low level of physical activity, low psychological well-being, high level of perceived stress and poor self-rated health (Table 7).

Table 7
Odds ratios (OR) of co-existing migraine, tension-type headache and neck pain and health-related variables controlled for educational attainment, Study II.

	OR[a] (95% CI)	*p*-value	OR[b] (95% CI)	*p*-value
Physical activity[c]				
High	Ref		Ref	
Moderate	2.5 (1.28 – 4.91)	0.007	2.7 (1.35 – 5.36)	0.005
Low	4.7 (1.79 – 12.55)	0.002	4.4 (1.62 – 11.72)	0.004
Missing, n	16			
Psychological well-being ≤ 50[d]				
No	Ref		Ref	
Yes	8.8 (4.19 – 18.36)	<0.001	9.3 (9.35 – 19.86)	<0.001
Missing, n	1			
Stress[e]				
Low	Ref		Ref	
Moderate	1.8 (0.89 – 3.73)	0.103	1.6 (0.74 – 3.32)	0.238
High	5.2 (2.48 – 10.96)	<0.001	6.0 (2.78 – 12.98)	<0.001
Missing	1			
Poor self-rated health[f]				
No	Ref		Ref	
Yes	39.2 (13.32 – 115.15)	<0.001	37.7 (12.77 – 111.52)	<0.001

CI = confidence interval, OR = odds ratio, Ref = reference value.
[a]OR = unadjusted.
[b]OR = adjusted for educational attainment.
[c]Assessed using the International Physical Activity Questionnaire (IPAQ short form) low, moderate and high physical activity was based on time and energy expenditure in the past 7 days.
[d]Assessed using the World Health Organisation five-item Well-Being Index (WHO-5) sum score from 0-100; sores ≤ 50 indicate poor psychological well-being.
[e]Assessed using stress scores with end-points 0 = no stress at all and 10 = very high degree of stress; scores 0-3 = low, scores 4-6 = moderate, scores 7-10 = high stress.
[f]Assessed using self-rated health with end-points 1 = very poor to 5 = very good; scores 1-3 indicated poor self-rated health.
The analyses were conducted by binary logistic regression and estimated as OR and 95% CI.

The ability to perform physical activity was highly reduced owing to migraine (median score of 9 on a rating scale from 0-10), moderately reduced owing to TTH (median 5) and less reduced owing to NP (median 3).

Almost half of the persons with migraine and co-existing TTH and NP (48%) rated migraine as the most burdensome of the three conditions. TTH was rated as the most burdensome condition by 30%, and NP was rated as the most burdensome condition by 10%. Migraine and TTH were rated as equally burdensome by 6%, all three conditions as equally burdensome by 3% and TTH and NP by 3%.

Effects of aerobic exercise on migraine and co-existing TTH and NP and pain perception (Studies III and IV)

Clinical characteristics are shown in Table 8.

Table 8
Clinical characteristics of included persons with migraine and co-existing tension-type headache and neck pain, Studies III and IV.

	Exercise (*N* = 26)	**Control (*N* = 26)**	**Discontinued (*N* = 18)**
Sex Women Men	 23 (88%) 3 (12%)	 23 (88%) 3 (12%)	 16 (89%) 2 (11%)
Age (years)	42 ± 10.9	36 ± 10.1	33 ± 11.9
Migraine duration (years)	20.4 ± 11.5	19.3 ± 14.5	13.6 ± 6.5
TTH duration (years)	17.8 ± 12.0	19.3 ± 12.9	17.8 ± 11.0
NP duration (years)	15.2 ± 13.4	15.6 ± 15.7	17.8 ± 12.2
Chronic migraine	9 (35%)	9 (35%)	7 (39%)
Chronic tension-type headache	2 (8%)	2 (8%)	3 (17%)
Chronic neck pain	13 (50%)	11 (42%)	12 (67%)
Migraine without aura	21 (81%)	19 (73%)	9 (50%)
Migraine with aura	0	2 (8%)	2 (11%)
Migraine with and without aura	5 (19%)	5 (19%)	7 (39%)
Baseline, preventive medication[a]	10 (38%)	9 (35%)	5 (28%)
Treatment period, preventive medication[a]	12 (46%)	14 (54%)	-
Follow-up, preventive medication[a]	10 (38%)	10 (38%)	-

Numbers are presented as mean ± SD or number (%).
[a]Beta blockers (used by 19% in exercise group, 12% in control group at baseline) and other preventives (topiramate, angiotensin II blockers, amitriptyline, catapressan and riboflavin).

There were no significant differences between included participants in exercise and control groups with regards to clinical characteristics. A significant difference in age was found between exercise and control groups among those who completed the study. There were no significant differences between the participants who completed the study and those who discontinued with regards to age, sex and chronic pain.

During the study period, there were no significant differences between groups and within groups with regards to intake of preventive and acute medication.

Primary endpoints

No between-group differences were found for migraine days and total tenderness score tenderness (Table 9, 11). A significant within-group reduction for exercise group was observed for migraine days after treatment from 9.2 to 7.2 days (p = 0.025) this result was also observed at follow-up (p = 0.005) (Table 9). A significant within-group reduction for exercise group was observed for total tenderness score at end of treatment from 24 to 20 (p = 0.017) (Table 11). At follow-up the total tenderness score was 19.5 but not statistically significant compared to baseline (p = 0.30) (Table 11).

Table 9
Migraine, tension-type headache and neck pain variables, physical fitness, level of physical activity and well-being after 3-month treatment and at follow-up (six months from baseline), Study III.

	Exercise *N* = 26			**Control *N* = 26**			**Between groups[a]**	**Between groups[a]**	**Within exercise[b]**		**Within control[b]**	
	Baseline	Treatment end	Follow-up	Baseline	Treatment end	Follow-up	Baseline vs treatment end	Baseline vs follow-up	Baseline vs treatment end	Baseline vs follow-up	Baseline vs treatment end	Baseline vs follow-up
Migraine							*p*-value[c] (95% CI)	*p*-value[c] (95% CI)	*p*-value[c]	*p*-value[c]	*p*-value[c]	*p*-value[c]
Days	9.2 (5.2)	7.2 (5.8)	7.2 (4.9)	8.3 (4.0)	7.7 (4.9)	7.2 (4.7)	0.23 (-0.95 – 3.88)	0.33 (-1.31 – 3.80)	0.025[e]	0.005[e]	0.44	0.40
Pain intensity	5.6 (1.8)	4.5 (2.4)	4.7 (2.1)	5.7 (1.8)	5.1 (2.1)	5.1 (2.1)	0.33 (-0.60 – 1.75)	0.58 (-0.84 – 1.48)	0.005[e]	0.028[e]	0.24	0.098
Duration in hours	104.9 (83.6)	80.9 (90.7)	75.7 (69.1)	90.3 (67.5)	78.9 (68.0)	74.1 (72.9)	0.42 (-0.25 – 0.59)	0.39 (-20.71 – 52.30)	0.045[e]	0.035[e]	0.20	0.23
AUC[d]	734.6 (661.0)	565.3 (778.7)	568.0 (628.5)	652.2 (577.3)	531.8 (583.2)	490.3 (551.8)	0.46 (-0.30 – 0.67)	0.85 (-245.08 – 294.61)	0.034[e]	0.083	0.096	0.062
Tension-type headache												
Days	7.6 (6.5)	8.3 (8.2)	7.9 (7.6)	7.9 (5.9)	7.3 (8.0)	7.2 (8.9)	0.22 (-3.51 – 0.82)	0.28 (-0.81 – 0.24)	0.28	0.67	0.48	0.21
Pain intensity	2.8 (1.2)	2.5 (1.5)	2.4 (1.6)	3.1 (1.6)	2.7 (0.3)	2.4 (2.0)	0.80 (-1.41 – 0.31)	0.31 (-1.36 – 0.44)	0.44	0.28	0.13	0.042[e]
Duration in hours	90.3 (112.9)	94.5 (128.8)	81.94 (102.4)	94.2 (103.8)	98.3 (145.5)	87.0 (147.7)	0.22 (-0.89 – 0.21)	0.44 (-42.29 – 18.79)	0.42	0.81	0.90	0.24
AUC[d]	321.6 (409.9)	334.3 (422.2)	293.5 (366.6)	442.2 (591.9)	531.4 (944.9)	455.9 (842.3)	0.19 (-1.05 – 0.21)	0.32 (-0.94 – 0.32)	0.49	0.74	0.59	0.27
Neck pain												
Days	17.2 (8.4)	18.0 (9.7)	14.5 (11.1)	15.0 (9.3)	13.8 (10.7)	14.4 (11.1)	0.77 (-0.39 – 0.29)	0.40 (-2.19 – 5.44)	0.77	0.12	0.49	0.31
Pain intensity	4.5 (1.4)	3.9 (1.8)	3.7 (2.3)	4.0 (1.5)	3.6 (2.2)	3.6 (2.0)	0.73 (-0.84 – 1.19)	0.40 (-0.54 – 1.33)	0.045[e]	0.007[e]	0.59	0.23
Duration in hours	224.5 (156.6)	272.5 (174.9)	194.6 (179.6)	191.4 (148.6)	183.6 (177.4)	208.3 (211.1)	0.26 (-0.67 – 0.18)	0.89 (-0.47 – 0.55)	0.22	0.48	0.59	0.71
AUC[d]	1126.1 (918.2)	1309.2 (1056.4)	1007.4 (1166.4)	983.0 (939.3)	886.4 (1941.7)	1010.8 (1132.5)	0.18 (-693.92 – 134.48)	0.55 (-289.14 – 534.62)	0.50	0.44	0.59	0.73
Acute medication intake in days	7.4 (4.0)	5.9 (3.7)	6.7 (2.9)	6.0 (3.4)	6.2 (3.9)	5.5 (4.2)	0.14 (-0.53 – 3.84)	0.61 (-1.47 – 2.47)	0.11	0.22	0.94	0.38

VO_{2max}[f]	31.6 (8.9)	35.5 (10.2)	32.7 (9.2)	35.2 (8.7)	33.3 (8.5)	33.7 (9.1)	0.005[e] (-9.34 – -1.84)	0.29 (-7.50 – 2.31)	0.014[e]	0.31	0.22	0.48
MET-minutes/ week[g]	2261.6 (2161.6)	3348.4 (2679.1)	3579.0 (3820.4)	2232.3 (1545.2)	1534.6 (1124.3)	1853.9 (1279.8)	0.013[e] (-3306.51 – -414.57)	0.033[e] (-1.72 – -0.08)	0.11	0.20	0.027[e]	0.30
Well-being[h]	37.5 (14.5)	59.5 (18.3)	57.8 (21.1)	40.0 (14.8)	56.0 (19.6)	55.0 (19.9)	0.14 (-15.93 – 2.26)	0.40 (-15.06 – 6.06)	<0.001	0.001	<0.001	<0.001

Numbers are presented as mean (Standard Deviation).
[a]Between-group differences were analysed by Independent Samples T-test from baseline to the end of treatment and from baseline to the end of follow-up.
[b]Within-group differences were analysed by Wilcoxon singed-rank test from baseline to the end of treatment and from baseline to the end of follow-up.
[c]P-value <0.05.
[d]AUC = area under the curve of duration x pain intensity.
[e]Significant result.
[f]Assessed using the Åstrand's submaximal bicycle test to estimate the maximum oxygen uptake (VO2max).
[g]Assessed using the International Physical Activity Questionnaire (IPAQ short form), MET-minutes/week equals the sum of walking, moderate and vigorous physical activity in minutes per week and multiplied by the metabolic equivalent task (MET) for each category.
[h]Assessed by the World Health Organization five-item Well-Being Index (WHO-5) sum score from 0-100; lower scores indicate lower well-being.

Secondary endpoints

Between-groups differences. Exercise group showed better physical fitness (p=0.005) and higher MET-minutes/week (p=0.013) compared to controls after the treatment period (Table 9). They also showed reduced burden of migraine in terms of improved ability to participate in household chores (p=0.028), paid work/study tasks (p=0.008), participate in family activities (p=0.012) and to engage in physical activity (p=0.004). Further, they improved the ability to engage in physical activity because of reduced impact of TTH (p=0.001), and in household chores (p=0.028) and paid work/study tasks (p=0.018) because of reduced impact of NP (Table 10).

An increase in MET-minutes/week (p=0.033), (Table 9), and improvements in the ability to perform daily activities because of migraine were also observed from baseline to follow-up (Table 10). The ability to engage in household chores (p=0.022) and physical activity (p=0.042) because of reduced impact of TTH and physical activity because of NP (p=0.004) was improved from baseline to follow-up (Table 10).

There were no between-group differences for local tenderness, pressure pain thresholds, pain rating of supra-threshold pressure pain, electrical pain threshold, pain rating of electrical pain supra-threshold and temporal summation (Table 11, 12 and 13).

Table 10

The ability to engage in daily activities owing to migraine, tension-type headache and neck pain after 3-month treatment and at follow-up (six months from baseline), Study III.

	Exercise *N* = 26			**Control** *N* = 26			**Between groups[a]**	**Between groups[a]**	**Within exercise[b]**		**Within control[b]**	
	Baseline	Treatment end	Follow-up	Baseline	Treatment end	Follow-up	Baseline vs treatment end	Baseline vs follow-up	Baseline vs treatment end	Baseline vs follow-up	Baseline vs treatment end	Baseline vs follow-up
							p-value[c] (95% CI)	*p*-value[c] (95% CI)	*p*-value[c]	*p*-value[c]	*p*-value[c]	*p*-value[c]
Variables 0-10[d]												
Migraine												
Household chores	6.6 (2.4)	4.5 (3.4)	5.0 (3.5)	5.8 (2.6)	5.3 (2.8)	5.8 (2.8)	0.028[g] (0.22 – 3.60)	0.039[g] (0.09 – 3.33)	0.002[g]	0.010	0.45	1.00
Paid work/study tasks	7.0 (2.7)	4.3 (3.3)	4.8 (3.4)	5.4 (2.6)	5.7 (3.2)	6.3 (2.9)	0.008[g] (0.68 – 4.28)	0.002[g] (1.14 – 4.68)	0.001[g]	0.001[g]	0.77	0.27
Social activities[e]	6.8 (3.1)	4.7 (3.5)	5.2 (3.7)	5.9 (3.3)	5.2 (2.8)	6.7 (3.2)	0.17 (-0.71 – 3.84)	0.050 (-0.002 – 4.30)	0.016[g]	0.048[g]	0.30	0.54
Family life[f]	6.5 (2.5)	4.2 (3.5)	4.9 (3.3)	4.7 (2.8)	4.6 (2.7)	5.9 (2.9)	0.012[g] (0.55 – 4.14)	0.002[g] (1.09 – 4.51)	0.001[g]	0.021[g]	0.94	0.038[g]
Physical activity	8.0 (2.9)	5.1 (3.8)	5.6 (3.6)	6.8 (3.0)	6.2 (3.4)	6.9 (2.9)	0.004[g] (0.96 – 4.82)	0.002[g] (1.26 – 5.13)	<0.001[g]	0.001[g]	0.74	0.58
Tension-type headache												
Household chores	4.2 (2.4)	3.9 (2.5)	2.8 (2.7)	3.6 (2.3)	3.3 (2.5)	3.6 (2.3)	0.54 (-0.93 – 1.75)	0.022[g] (0.26 – 3.28)	0.18	0.001[g]	0.64	0.74
Paid work/study tasks	4.6 (2.4)	3.3 (2.6)	2.8 (2.1)	3.6 (2.0)	3.8 (2.7)	3.7 (2.3)	0.11 (-0.26 – 2.45)	0.10 (-0.29 – 3.08)	0.023[g]	0.014[g]	0.92	0.61
Social activities[e]	4.8 (2.5)	4.1 (3.1)	3.2 (2.9)	3.8 (2.6)	3.6 (2.9)	3.5 (2.5)	0.41 (-1.03 – 2.48)	0.29 (-0.93 – 3.06)	0.12	0.021[g]	0.58	0.25
Family life[f]	4.0 (2.2)	3.5 (3.0)	2.4 (2.7)	3.2 (2.4)	2.9 (2.5)	3.1 (2.1)	0.50 (-0.98 – 1.96)	0.11 (-0.33 – 3.25)	0.18	0.007[g]	0.66	0.58
Physical activity	6.4 (2.8)	4.0 (2.7)	3.3 (3.2)	5.3 (3.5)	5.4 (3.5)	4.5 (2.9)	0.001[g] (1.24 – 4.29)	0.042[g] (0.08 – 3.94)	0.001[g]	<0.001[g]	0.29	0.047[g]
Neck pain												
Household chores	3.0 (2.6)	2.0 (2.2)	2.3 (2.7)	2.2 (2.0)	2.3 (2.4)	2.5 (2.3)	0.028[g]	0.11	0.022[g]	0.23	0.47	0.15

							(0.12 – 2.10)	(-0.27 – 2.59)				
Paid work/study tasks	3.0 (3.1)	1.7 (1.6)	2.1 (2.4)	2.1 (1.7)	2.4 (2.1)	2.4 (2.2)	0.018[g] (0.22 – 2.23)	0.21 (-0.57 – 2.56)	0.17	0.56	0.030[g]	0.11
Social activities[e]	2.4 (2.7)	1.7 (2.0)	1.6 (2.6)	1.8 (1.9)	1.9 (2.5)	2.4 (2.4)	0.37 (-0.65 – 1.72)	0.18 (-0.48 – 2.43)	0.18	0.23	0.78	0.52
Family life[f]	2.2 (2.7)	1.6 (2.0)	1.3 (2.2)	1.6 (1.8)	1.7 (2.0)	2.1 (1.9)	0.29 (-0.48 – 1.57)	0.14 (-0.35 – 2.38)	0.15	0.15	1.00	0.63
Physical activity	3.8 (2.9)	2.0 (2.0)	1.8 (3.1)	3.2 (2.5)	3.2 (2.8)	3.9 (3.2)	0.073 (-0.14 – 2.96)	0.004[g] (1.04 – 4.80)	0.006[g]	0.013[g]	0.92	0.19

Numbers are presented as mean (Standard Deviation).
[a]Between-group differences were analysed by Independent Samples T-test from baseline to the end of treatment and from baseline to the end of follow-up.
[b]Within-group differences were analysed by Dependent Samples T-test from baseline to the end of treatment and from baseline to the end of follow-up.
[c]P-value <0.05.
[d]Variables were rated on an 11-point numeric rating scale with the end points 0=no impact and 10=most imaginable impact.
[e]Social activities not including family activities.
[f]Participation in family activities.
[g]Significant result.

Within-group differences. In the exercise group, there was significant reduction for migraine pain intensity (*p*=0.005), migraine duration (*p*=0.045), migraine AUC (*p*=0.034) and in NP intensity (*p*=0.045) from baseline to the end of treatment. Migraine variables and NP intensity were also reduced from baseline to follow-up except for migraine AUC. Physical fitness (*p*=0.014) and psychological well-being (*p*<0.001) improved significantly from baseline to the end of treatment. Psychological well-being was also significantly improved at follow-up (Table 9). The ability to engage in all daily activities was significantly improved because of reduced impact of migraine, and for some activities because of reduced impact of TTH and NP after treatment and at follow-up (Table 10).

There were no within-group changes at the end of treatment for exercise group, but a significant increase in pressure pain threshold for splenius muscle (*p*=0.022) and for second finger (middle phalanx) (*p*=0.041) at follow-up (Table 12). Also, a significant increase was found in supra-threshold pain rating for single electrical stimulation of the tibial muscle (*p*=0.014) for exercise group at follow-up indicating an aggravation (Table 13). However, the pain threshold for tibial muscle measured in mA did not change in any of the three time points and the same tendency for both measures was also seen in control group (Table 13).

Table 11

Total tenderness and local tenderness score in persons with migraine and co-existing tension-type headache and neck pain of the exercise group (*n* = 26) and the control group (*n* = 26) after 3-month treatment and at follow-up (six month from baseline), Study IV.

	Total tenderness score (0-48) [a]	**Local tenderness, Splenius muscle (0-100 mm VAS)**[b]
Exercise group		
Baseline	24.0 (17.5, 30.5)	32.5 (9.5, 53.8)
End of three-month treatment	20.0 (10.8, 28.0)[c]	26.5 (6.5, 40.0)
End of follow-up	19.5 (14.0, 29.3)	28.8 (8.0, 51.3)
Control group		
Baseline	20.0 (7.8, 31.3)	8.3 (3.2, 41.6)
End of three months treatment	16.5 (9.0, 27.3)	12.7 (1.0, 51.3)
End of follow-up	17.0 (6.8, 27.5)	27.2 (4.5, 67.1)[c]

Numbers are presented as median values (first and third quartiles).

[a]Total tenderness scoring was measured by manual palpation of eight pairs of muscles of face, neck and shoulders, scores ranging from 0-48 (0 = no tenderness).

[b]Local tenderness score was measured by an algometer. Pain was scored on 0-100 mm VAS (0 = no pain).

[c]P-value <0.05 compared with baseline (analysed by the Wilcoxon signed rank test).

No between-group differences were found (analysed by the Mann-Whitney U-test).

Table 12
Pressure pain thresholds and pain ratings for supra-threshold pressure pain in persons with migraine and co-existing tension-type headache and neck pain of the exercise group (*n* = 26) and the control group (*n* = 26) at the end of three-month treatment and at the end of follow-up (six months from baseline), Study IV.

	Pressure pain thresholds				Supra-threshold pressure pain		
	Splenius muscle (kPa/cm^2)	Temporal muscle (kPa/cm^2)	Second finger (kPa/cm^2)		Splenius muscle (0-100 mm VAS)	Temporal muscle (0-100 mm VAS)	Second finger (0-100 mm VAS)
Exercise group							
Baseline	183.3 (140.3, 273.8)	135.3 (105.7, 170.7)	170.7 (132.2, 304.7)		39.0 (15.2, 62.5)	47.3 (25.2, 64.8)	23.7 (11.0, 36.7)
End of three months treatment	235.0 (145.2, 293.5)	138.3 (90.0, 172.7)	200.7 (140.8, 291.2)		47.7 (20.7, 55.6)	53.0 (33.0, 69.7)	31.9 (14.1, 46.4)
End of follow-up	253.3 (161.5, 318.0)[a]	148.0 (116.0, 171.5)	263.0 (183.2, 315.7)[a]		42.7 (24.5, 65.8)	57.5 (32.9, 73.3)	35.8 (12.7, 43.6)
Control group							
Baseline	207.3 (139.5, 258.5)	144.7 (111.5, 178.3)	213.7 (147.8, 267.8)		41.0 (20.5, 62.8)	55.2 (31.0, 70.3)	25.0 (7.0, 37.5)
End of three months treatment	218.0 (125.3, 299.7)	166.0 (109.7, 194.3)	233.3 (140.3, 287.0)		28.7 (17.7, 63.7)	45.3 (32.0, 67.2)	23.2 (14.1, 44.5)
End of follow-up	217.3 (156.0, 257.3)	136.0 (98.3, 170.3)	202.0 (143.0, 304.0)		41.7 (24.8, 57.7)	53.3 (41.7, 71.3)	38.0 (18.3, 48.3)

Numbers are presented as median values (fist and third quartiles).
[a]P-value <0.05 compared with baseline (analysed by the Wilcoxon signed rank test).
No between-group differences were found (analysed by the Mann-Whitney U-test).

Table 13
Pain thresholds for electrical stimulation and pain ratings for supra-threshold stimulation with single and repetitive stimuli in migraine and co-existing tension-type headache and neck pain of the exercise group (n = 26) and the control group (n = 26) at the end of three-month treatment and at the end of follow-up (six months form baseline), Study IV.

	Pain threshold Single electrical stimulus			**Supra-threshold pain score Single electrical stimulus**			**Supra-threshold pain score Repetitive electrical stimuli**	
	Splenius muscle (mA)	Tibial muscle (mA)		Splenius muscle (0-100 mm VAS)	Tibial muscle (0-100 mm VAS)		Splenius muscle (0-100 mm VAS)	Tibial muscle (0-100 mm VAS)
Exercise group								
Baseline	1.8 (1.2, 3.2)	2.3 (1.1, 3.2)		17.7 (7.8, 34.3)	9.5 (5.6, 23.1)		27.7 (11.3, 56.3)	20.8 (8.5, 45.5)
Treatment	2.2 (1.6, 2.8)	2.3 (1.7, 2.5)		20.0 (7.3, 32.2)	15.5 (4.2, 28.8)		32.3 (11.5, 53.3)	29.0 (9.3, 46.1)
Follow-up	2.0 (0.8, 3.1)	2.5 (1.8, 3.3)		11.3 (6.8, 43.3)	16.3 (6.3, 36.6)[a]		22.3 (6.4, 50.3)	32.2 (14.5, 45.8)
Control group								
Baseline	1.8 (1.4, 3.0)	2.0 (1.5, 3.5)		18.0 (5.4, 33.9)	11.3 (3.3, 26.0)		30.8 (11.2, 52.0)	24.0 (6.8, 47.3)
Treatment	1.7 (0.9, 3.2)	2.0 (1.3, 2.8)		21.3 (6.1, 42.9)	20.8 (7.2, 30.2)		33.5 (11.0, 59.7)	33.0 (16.3, 49.4)
Follow-up	1.8 (1.4, 3.2)	2.3 (1.6, 3.2)		18.8 (10.0, 37.7)	18.5 (10.3, 30.2)		28.2 (15.0, 62.1)	38.8 (12.2, 54.0)

Numbers are presented as median values (fist and third quartiles).
[a]P-value <0.05 compared with baseline (analysed by the Wilcoxon signed rank test).
No between-group differences were found (analysed by the Mann-Whitney U-test).

The post hoc analyses (Study III)

The post hoc analyses of days with migraine in chronic and episodic migraine respectively showed no differences between exercise group and control group. Within exercise group, the changes of days with migraine from baseline to the end of treatment and from baseline to follow-up in chronic migraine decreases were observed from 16 to 11 days (31%; *p*=0.19) and from 16 to 9 days (44%; *p*=0.018) respectively. In episodic migraine, decreases were observed from 7 to 6 days (14%; *p*=0.12) and from 7 to 5 days (29%; *p*=0.098) respectively (Figure 6).

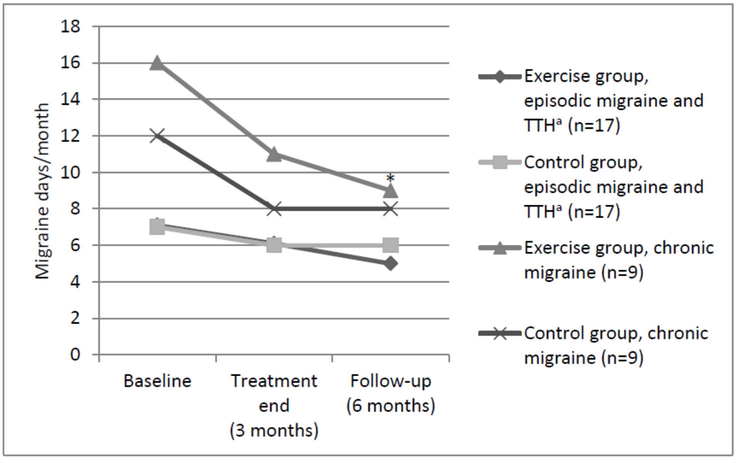


Figure 6
Median changes in migraine frequency in days per months from baseline to end of treatment and to follow-up (six months from baseline).
[a]TTH=tension-type headache
*p<0.05
Within exercise group
Chronic migraine, baseline to end of treatment (p=0.19); baseline to follow-up (p=0.018).
Episodic migraine and TTH, baseline to end of treatment (p=0.12); baseline to follow-up (p=0.098).
Within control group
Chronic migraine, baseline to end of treatment (p=0.31); baseline to follow-up (p=0.48).
Episodic migraine and TTH, baseline to end of treatment (p=0.96); baseline to follow-up (p=0.64).

Post hoc analyses (Study IV)

There were no changes observed for responders from baseline to the end of treatment for any of the applied measures. In contrast, a significant decrease in total tenderness score was observed from baseline to the end of treatment for non-responders from median 23 to 14 (39%; *p*=0.028).

The analyses of total tenderness score in chronic and episodic migraine, respectively, showed no differences between exercise and control groups. A significant within-group decrease was found for exercise group for episodic migraine from baseline to the end of treatment in median total tenderness score from 22 to 13 (41%; p=0.027). There were no other significant within-group changes observed for chronic and episodic migraine, respectively.

The exercise group reported no side effects caused by training.

Main discussion

The aims of this thesis were to develop and test a questionnaire for face and content validity together with additional questionnaires which in all assess the impact of migraine and co-existing TTH and NP; to investigate the prevalence of TTH and NP in persons with migraine and their impact of disease; and to investigate the effects of aerobic exercise for persons with migraine and co-existing TTH and NP. The main results are discussed below.

Development and validation of questionnaires assessing impact of migraine and co-existing TTH and NP (Study I)

Most items of the Impact M-TTH-NP were well understood, clear, and perceived as relevant and meaningful by the group-participants. Several of them perceived the items concerning sick leave and reduced productivity at work/school, measured in hours, as difficult to answer but relevant and meaningful. The group-participants also found it difficult to foresee the ability to do the current job two years from now. One explanation may be that they had suffered from headache and NP for several years and consequently were unable to predict their future symptoms. Also, several group-participants thought it was difficult to rate the impact of headache and NP in general, as they were used to do their daily tasks despite pain. These factors may be explained by a typical coping strategy among persons with chronic headache that involves avoidance behaviour and endurance strategies (45). Such compensatory mechanisms were not covered in the applied instruments. The nine items that did not reach the cut off levels for either excellent I-CVI and/or acceptable AD index assessed clinically relevant aspect, but will need further revision and analyses.

Andrée et al. have also developed a large multi-dimensional questionnaire “The EUROLIGHT Questionnaire” to estimate the burden of headache disorders (107). This questionnaire has been tested for face and content validity and obtained acceptable construct validity. The EUROLIGHT Questionnaire and our newly developed questionnaire cover some similar items e.g. the use of healthcare services, medication intake, headache impact, absenteeism and reduced productivity. However, The EUROLIGHT Questionnaire does not differentiate between migraine and TTH and it does not contain items about NP and physical activity.

The selected additional questionnaires have previously been tested for validity. IPAQ and MSQ were the only questionnaires that did not obtain excellent S-CVI/Ave. In line with our results, IPAQ has been reported to have a weak concurrent validity, but also a fair to moderate criterion validity (86, 108, 109). In contrast to our study, the construct validity and ability to detect change of MSQ v. 2.1 has been established (88, 110). Our findings of an excellent content validity were in line with previous studies, thus, a review has reported WHO-5 to have an excellent validity (111). MDI as a diagnostic tool to diagnose and monitor depression among depressive persons has been found to have highest coefficient values in relation to Beck Depression Inventory and Hamilton Depression Scale (112). Finally, The NDI has shown adequate measurement properties (113). In contrast to the present study, NDI obtained poor content validity, in a recent study of NP-patients (114) because of unclear definition of the construct.

Most group-participants and headache experts found the additional questionnaires relevant except from IPAQ which received most critical comments especially concerning the way in which the questionnaire quantifies the activities. MSQ was perceived as redundant by some experts, which may explain why MSQ did not obtain excellent SCV-I/Ave.

Prevalence and impact of migraine and co-existing TTH and NP (Study II)

The prevalence of migraine with co-existing TTH and NP was lower than the findings from the population-based study by Ashina et al. (6) that found a one-year prevalence of NP of 89.3% in persons suffering from migraine and co-existing TTH. The difference may be due to the sub-grouping of participants applied by Ashina et al. that investigated NP in persons with migraine and co-existing TTH. We investigated co-existing TTH and NP in persons with migraine. Molarius and Tegelberg (42) reported findings similar to ours although their case ascertainment was not based on ICHD-criteria.

In accordance with our study Varkey et al. (64) found that persons with migraine were less physically active compared to headache-free individuals and low physical activity was associated with a higher prevalence of migraine. Interestingly, the population-based study by Ashina et al. (115) found that low physical activity was associated with migraine and co-existing TTH to a higher degree compared to other types of headache and the association was stronger with TTH than migraine only.

The characteristics of our participants with migraine and co-existing TTH and NP reflect the findings of other studies on the impact of migraine on psychological well-being, an association with increased stress and poor self-rated health (35, 36, 41, 42). Schramm et al. (41) did not find any differences in the level of perceived stress between those with migraine only and those with migraine and co-existing TTH. Molarius and Tegelberg (42) found that persons with migraine and recurrent headache reported poorer self-rated health than those with migraine only. Reduced psychological well-being may indicate stress or depression (37). Persons with migraine are in general very susceptible to stress (39, 40) and have higher levels of stress compared to headache-free individuals (41) which is in line with our findings.

Our results suggest that persons with migraine and co-existing TTH and NP may have more barriers to perform physical activity compared to those with migraine only, even though TTH and NP were not rated as quite as burdensome. Decreased psychological well-being, high level of perceived stress and low self-rated health among those with migraine and co-existing TTH and NP suggest conditions that may make it more difficult to motivate this group to increase their levels of physical activity.

Effects of aerobic exercise on migraine and co-existing TTH and NP and pain perception (Studies III and IV)

Earlier RCT studies have investigated the effects of aerobic exercise for persons with migraine (20, 21, 69). The applied methodologies differed from ours and the results are, therefore, difficult to compare; e.g. one study had active control groups (21), another study used mixed treatment strategies (20), and another studied unsupervised aerobic exercise for persons with chronic migraine (69). However, the improvement of migraine in our exercise group is in line with the conclusion of the systematic review and meta-analyses by Luedtke et al. (19). Previous studies have found that the prognosis of migraine may deteriorate with co-existing TTH (24), and that NP was a predictor of disability in migraine (25). Consequently, all three conditions need to be addressed and may require different treatment strategies.

Although the cause effect relationship is unclear, a certain level of physical fitness may be needed to reduce migraine frequency over time, as suggested by Hagen et al., in a cross-sectional study, which linked high level of physical fitness with lower migraine prevalence (65).

In our study, both groups significantly improved their psychological well-being. Improvement of the control group is likely a time effect phenomenon and/or positive expectations of future treatment (116) since the control group was offered individual tailored physiotherapy after follow-up.

The effects of regular aerobic exercise on migraine and co-existing TTH and NP may be explained by positive alteration of avoidance behaviour (43-45). These strategies may be related to daily activities and by increased well-being, which is a known effect of physical activity (61), rather than affecting the pain modulating system measured by muscle tenderness and pain thresholds.

Previous RCT-studies investigating the effect of aerobic exercise have found a decrease in migraine pain intensity (20, 21, 69). However, these studies did not investigate the effect on central pain mechanisms which make comparison of our results difficult. Koseoglu et al. (67) have suggested that increased release of beta-endorphins caused by physical activity could have an analgesic effect on migraine. Our results do not support this hypothesis.

In contrast to the present study, Naugle et al. (72) found that moderate to vigorous physical activity performed for seven consecutive days was associated with less temporal summation of pain in healthy adults, and that self-reported vigorous physical activity, measured by IPAQ, exhibited less temporal summation of pain and greater conditioned pain modulation, also, in healthy adults (73). On the other hand, in agreement with our results, Jones et al. (74) did not show an effect of six weeks moderate to vigorous aerobic exercise on pressure pain thresholds, but found an improvement of ischemic pain tolerance in healthy adults. Also, in line with our results, Smith et al. (75) reported that the acute effect of 30 minutes of moderate aerobic exercise did not induce hypoalgesia in persons with chronic whiplash associated disorders measured by pressure pain thresholds. In contrast, Hooten et al. (76) showed an improvement of three weeks aerobic exercise on pain thresholds in persons with fibromyalgia. Thus, the acute and long term effects of aerobic exercise on pain perception are still not clear.

Methodological considerations

Internal and external validity

All four studies have high internal validity. Headache diagnoses were based on headache diaries, detailed headache history, headache and NP interviews and examinations by neurologists (Studies I-IV) and a physiotherapist (Studies I, III and IV). Important secondary headaches were excluded. All participants were classified according to the ICHD-3 beta criteria (7). Frequency of headache and NP, pain intensity, duration and acute medication intake were measured and reported by the participants as previously recommended (77) (Studies III and IV).

As most of the participants in all four studies were recruited from a tertiary referral headache centre external validity may be limited as they may suffer from a higher frequency of headache and NP compared to less specialized clinics. Also, a large proportion of the participants suffered from chronic headaches.

All headache experts (Study I) had a high expertise and were recruited from the same tertiary referral headache centre, which could have resulted in selection bias. However, none of the experts were involved in the development of the new questionnaire.

Most healthy controls were recruited among healthcare professionals (Study II), and were generally more highly educated and more physically active than persons with migraine and co-existing TTH and NP. Also, they were more physically active than the general population (117). However, they were very close to the general population regarding sum scores of psychological well-being (118).

Self-reported data

Self-reported data may, to some extent, suffer from recall bias especially if the recall period is too long. The use of questionnaires allows for collecting a larger amount of information and is less time consuming than personal interviews. Nevertheless, a personal interview may be better than self-report in reducing recall bias, and might have prevented the exclusion of participants who had inadequate answers in the IPAQ questionnaire. The drawback is that an interview may cause interviewer bias. Previously studies on the IPAQ have reported this questionnaire to overestimate time spent on physical activity (109, 119). This may be caused by social desirability bias or simply by difficulty in remembering how much time is spent on different activities.

With regards to headache and NP interviews, prospective diary recordings of these combined conditions supplemented with the interview may have been more ideal as diagnostic tools to ascertain multiple diagnoses (120) (Studies I and II). Finally, the impact of headache and NP is a comprehensive topic which requires one large or several questionnaires to investigate this topic. Filling out a large number of questionnaires may have been overwhelming both for participants (Studies I-IV) and for headache experts (Study I) and thereby influencing the results.

The ability to perform daily activities despite pain (as discovered in Study I) may have an important implication for the quantification of the effect of future treatment modalities, as many persons with headache have lived with pain for many years and may underreport disability simply because they have become accustomed to it.

Content and face validity

To quantify content validity (Study I) the CVI was applied as previously used (121). S-CVI average approach was used as recommended (103, 104) as it represents information about each item compared to the universal agreement approach, which is considered to be too stringent as the chance of universal agreement decreases with the increasing number of experts (103, 104). The I-CVI does not account for chance agreement among raters, and the analysis of the collapsed response categories may lead to loss of information (122). The AD index was therefore applied as used in an earlier study (121). This index provided information of all four response categories as opposed to I-CVI which collapsed the response categories into relevant and not relevant.

There is, to the best of our knowledge, no agreed consensus with regards to the methods of obtaining face validity. We chose group interviews which gave good indications about participants' perception of the questionnaires. The content validity approach could have been applied in order to quantify answers in addition to subjective feedback from participants as previously applied (114).

Risk of bias in the applied RCT-study

Randomization decreases the effect of possible confounding factors. Strict inclusion criteria reduce the risk of confounders even further. On the other hand, too strict criteria increase the risk of getting too far from known clinical practice; therefore, Studies III and IV were designed as an add-on treatment and did not make any demands for regulation of preventive medication in either group in order to reflect daily clinical practice. Also, there were no specified requirements with regards to level of physical activity before entering the study; this was to reflect a differentiated population.

Persons who were interested in physical activity as a treatment for headache were more likely to sign-up for such a study. These factors can have influenced the results.

The reason for dropping out of a study is important to address, because drop-outs' symptoms might have improved or worsened. However, we evaluated participants who improved, who did not have any change of symptoms, and who have worsened. We, therefore, believe our results to be realistic, but our results should obviously be confirmed in future studies.

Earlier reviews of the effect of exercise on persons with headache have recommended future studies to include a higher number of participants in order to increase power (19, 77); however, recruiting participants for these kinds of active interventions with a long follow-up period is rather challenging, costly and time consuming.

Participants in the control group were offered individually tailored physiotherapy after the study period instead of the standardised aerobic exercise program. This may have increased positive expectations of future treatment (116) and possibly affected several measures like psychological well-being. This phenomenon may often be of concern for RCT-studies investigating the effects of exercise as controlling for placebo is almost impossible. An active control group may reduce the risk of improvement owing to positive expectations if the aim of a study is to study the difference between different treatment strategies.

The persons who conducted the tests of physical fitness and QST (Studies III and IV) were not blinded to participants' grouping. This could have affected the results. However, this influence may have been limited with regards to the test of physical fitness, as the test was controlled by a software program which required stable heart rate and predetermined speed, otherwise the test would fail. With regards to QST, this may necessarily lead to a bias towards false positive results which were not the case in our study (Study IV); therefore, this influence may also have been limited.

The participants were allowed to continue with prescribed preventive and acute medication. However, they were not allowed to take acute medication on the day of testing. Also, there were no significant differences between groups and within groups with regards to intake of preventive and acute medication at any time point. We therefore believe this influence to be limited.

QST

We used a wide range of quantitative sensory tests to measure the effect of regular aerobic exercise at a moderate to vigorous intensity level on endogenous pain perception. These tests are widely used and elucidate several aspects of pain perception. Our results are rather consistent as none of the applied tests showed a difference between exercise group and control group at the different time points indicating that lack of power does not seem to be an explanation. The applied QST may not have been optimal or sensitive enough to detect a change over time with regards to a three-month aerobic exercise program on this population or the time window may have been too short.

Main conclusions

Development and validation of questionnaires assessing the impact of migraine and co-existing TTH and NP (Study I)

- The Impact of M-TTH-NP questionnaire had acceptable face validity and excellent content validity.
- The Impact of M-TTH-NP questionnaire can be supplemented with WHO-5 for measuring psychological well-being, MDI for additional questions regarding depression and NDI for measuring neck disability.

Prevalence and impact of migraine and co-existing TTH and NP (Study II)

- A large subset (67%) of a clinical sample of persons with migraine suffered from co-existing TTH and NP.
- Migraine and co-existing TTH and NP have a considerable impact on levels of physical activity, psychological well-being, perceived stress and self-rated health compared to healthy controls.

Effects of aerobic exercise on migraine and co-existing TTH and NP and pain perception (Studies III and IV)

- Aerobic exercise reduced the burden of migraine on the ability to engage in daily activities.
- The ability to engage in physical activity was improved owing to reduced impact of TTH and NP and for some additional daily activities owing to reduced impact of TTH.
- Frequency, pain intensity and duration of migraine were reduced in the exercise group.
- Aerobic exercise did not show any effect on the pain modulation system.

The Impact M-TTH-NP questionnaire can be used in clinical settings. A large subset of persons with migraine suffered from co-exiting TTH and NP, they were highly physically inactive and suffered from a large impact of disease. Aerobic exercise can improve the impact and severity of migraine, however, these effects cannot be explained by changes in the pain modulation system, but may rather be explained by positive alteration of avoidance behaviour and endurance strategies leading to improvement in the ability to engage in daily activities.

Clinical implications and future perspectives

- Using the Impact M-TTH-NP questionnaire may lead to a deeper understanding of the complexity of migraine with co-existing TTH and NP as this questionnaire covers information on pain, triggers, psychosocial, socioeconomic and work related aspects.
- The Impact M-TTH-NP questionnaire may be used in clinical settings both as a cross-sectional measurement and as a possible effect measure. As found in Study II, some of the items can show a difference between persons with headache and NP and a healthy population. Further, in Study III, the items concerning ability to engage in daily activities showed improvement over time and a difference between exercise and control groups.
- Persons with migraine and co-existing TTH and NP may require more individually tailored interventions to increase level of physical activity, and to improve psychological well-being, perceived stress and self-rated health.
- Aerobic exercise has been shown to be effective and safe to apply and should therefore be implemented as a physiotherapeutic treatment strategy in multidisciplinary specialized headache clinics.

Future perspectives

- Further investigation of validity and reliability of the Impact M-TTH-NP questionnaire is needed.
- A large subset of persons with migraine suffers from co-existing TTH and NP both in the population and in the clinic. Future studies are needed to investigate whether persons with migraine and co-existing TTH and NP suffer from a greater impact of disease compared to persons with migraine only.
- Aerobic exercise showed especially effect on migraine severity and migraine burden. Future studies are warranted to investigate additional

treatment strategies such as strength training for persons with the combination of migraine, TTH and NP.

- Anecdotal feedback from participants in the exercise group was predominantly positive with regards to the experience of the aerobic exercise program. It would, therefore, be interesting to investigate in more detail how aerobic exercise is experienced in persons with migraine and co-existing TTH and NP.
- This study did not reveal any effects on pain perception. The positive findings of aerobic exercise may be explained by positive alterations in avoidance behaviour. Future treatment studies may add measurements of coping strategies which involve avoidance behaviour and endurance strategies.
- For some persons it may be difficult to allocate time to engage in aerobic exercise three times a week. It would be interesting to study the effect of aerobic exercise twice a week with the same intensity and same duration as in the present study compared with aerobic exercise at a higher intensity and a shorter duration.

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