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Effectiveness of Exercise Interventions for Migraine

Systematized review

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ABSTRACT

Migraine is classified as a primary headache disorder among tension-type headaches, trigeminal autonomic cephalgias, and other primary headache disorders. Migraine affects many people during their lifetime being one of the leading causes of disability worldwide. Migraine has significant effects on individuals as well as economics on society.

The treatment of migraine relies on patient education and medical treatment. Lifestyle modifications and nonpharmacological treatments also have a role. As a worldwide prevalent disease, there is a need to have complementary treatments in addition to pharmacological treatments.

This thesis aimed to evaluate the effectiveness of exercise interventions for migraine in adult patients. The purpose was to summarize information about the benefits of exercise interventions to be helpful in education, clinical practice, and decision-making with migraine patients.

The method of this thesis was a systematized review. Systematic reviews of randomized controlled trials (RCTs) were included (N=3). Critical appraisal and content analysis was conducted. The results of this thesis indicated no statistically significant evidence of exercise effectiveness on migraine attack intensity and frequency. Few RCTs in the systematic reviews provide promising findings on the possible effectiveness of aerobic exercise on migraine intensity and attack frequency.

The results of this thesis indicate that aerobic exercise might be a beneficial option for nonpharmacological treatment. Exercise was shown not to have serious adverse effects in the included studies. In the future, high-quality randomized controlled studies are needed on the topic.

Keywords: migraine, effectiveness, exercise, physical activity, systematic review

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APPENDICES

1 INTRODUCTION

Migraine is classified as a primary headache disorder among tension-type headaches, trigeminal autonomic cephalgias, and other primary headache disorders. Migraine affects many people during their lifetime being one of the leading causes of disability worldwide. For individual patients, frequent migraine attacks impair the quality of life and ability to function. (Ailani et al. 2021, 1022; Headache Classification Committee of the International Headache Society 2018, 17–18; Steiner et al. 2020, 1, 3.)

Migraine treatment consists of treatment of acute migraine and preventive care. Migraine treatment is symptomatic treatment, as currently there is no curable treatment. Treatment of an acute migraine is mainly pharmacological. Prevention of migraine attacks consists of medication, lifestyle modification, and nonpharmacological treatment options. (Ailani et al. 2022, 1022; Jankovic et al. 2021, 1761–1762, Ropper et al. 2019, 195, 197.)

The Physical Activity Guidelines for Americans recommend regular endurance and strength training routines. Endurance training is recommended to be practiced for at least 150 minutes of moderate-intensity aerobic exercise or for 75 minutes of vigorous-intensity aerobic exercise per week for adults. Strength training for multiple muscle groups is recommended. Exercise has a well-documented effect on pain for different conditions. Aerobic exercise is the most studied exercise type for migraine treatment. It seems to be the most effective type of exercise for migraine, but there is no clear evidence of the superiority of one type of exercise. (Gross et al. 2015, 34; Hayden et al. 2021, 20; National Institute for Health and Care Excellence 2022, 8; Varangot-Reille et al. 2022, 7.)

As a worldwide prevalent disease, there is a need to have complementary treatments in addition to pharmacological treatments. This master’s thesis examined exercise interventions for migraine. This thesis aimed to evaluate the effectiveness of exercise interventions for migraine in adult patients using a systematized review method and content analysis. The purpose was to summarize information about the benefits of an exercise intervention to be helpful in education, clinical practice, and decision-making with migraine patients.

2 THEORETICAL FRAMEWORK

2.1 MIGRAINE

2.1.1 Diagnosis of Migraine

According to the International Classification of Headache Disorders (ICHD-3), migraine is classified as a primary headache disorder among tension-type headaches, trigeminal autonomic cephalgias, and other primary headache disorders. The most common types of migraine are migraine without aura and migraine with aura, as first mentioned is 5-fold more prevalent. Migraine diagnosis is ordinarily a clinical diagnosis; anamnesis and clinical examination are sufficient for diagnosis. Sometimes additional testing, e.g., imaging, cerebrospinal fluid tests, and/or blood tests are needed to rule out other causes of headache. Diagnostic criteria for migraine are presented in Table 1 and all migraine types in Appendix 1. (Headache Classification Committee of the International Headache Society 2018, 17–18; Jankovic et al. 2021, 252–253; Ropper et al. 2019, 185, 1759.)

Migraine attack without aura typically lasts between 4 and 72 hours and occurs repeatedly. The onset of the attack is often in the morning or during the daytime. Triggering factors can be rigorous physical activity or stress, hours or days before the attack. The typical symptom is unilateral headache in the frontotemporal area, associated with sensitivity to light (photophobia) and/or sounds (phonophobia). Dizziness, vertigo, and hearing loss are possible symptoms in migraine patients. One-third of attacks might produce bilateral headaches. In children and adolescents, bilateral presentation is the most common. Cutaneous allodynia and cranial autonomic symptoms might be present during the attack. Physical activity provokes symptoms. A small proportion of women have migraine associated with menstruation, these attacks tend to last longer and happen most likely without aura. Typically, patients have prodromal symptoms hours or days before a migraine attack. These symptoms include fatigue, neck symptoms, concentration difficulties, nausea, yawning, pallor, and sensitivity to light or sounds. After a migraine attack, patients may have tiredness, neck symptoms, concentration difficulties, and so-called postdromal symptoms. (Headache Classification Committee of the International Headache Society 2018, 17–19; Jankovic et al. 2021, 250, 277; Ropper et al. 2019, 181–182, 189.)

Aura is a combination of one or more neurologic symptoms that might happen before and/or during a migraine attack on patients who have migraine with aura. The prodromal phase occurs usually the day before, with symptoms including yawning, drowsiness, hunger or anorexia, and mood changes. A typical aura symptom is a visual symptom only in one eye, which presents as a first nearby point of fixation and may be laterally (left or right) spreading a “zigzag” figure called a fortification spectrum. Partial or absolute loss of vision field, scotoma, is present. Scotoma can exist without a fortification spectrum. Migraine with aura - patients can experience attacks without aura symptoms. The second most common aura symptoms are sensory. Paraesthesia, or pins and needles, appears unilaterally in the body, slowly changing area, still appearing only on the same side of the body. Rarely do patients have speech disturbances that are nonspecific or aphasic. The patient may experience several aura symptoms, typically one expression at a time, starting with visual, then progressing to sensory and speech disturbances. Aura symptoms last for an hour; however, motor symptoms can be longer lasting. Migraine with aura can have an onset at any time of day, with some patients typically in the morning. The above-mentioned clinical picture is classified as a migraine with a typical aura, although symptoms vary a lot from patient to patient. (Headache Classification Committee of the International Headache Society 2018, 20–21; Jankovic et al. 2021, 250; Ropper et al. 2019, 188–189.)

Migraine with brainstem aura and hemiplegic aura are subforms of migraine with aura. Brainstem aura includes symptoms originating from the brainstem (e.g., dysarthria, vertigo, tinnitus, hypoacusis, and diplopia), excluding motor weakness and retinal symptoms. Brainstem migraine attacks may include a faint, nonresponsiveness, or confused state, which can last for hours. Hemiplegic migraine is defined as when a patient has an aura symptom and motor weakness, which lasts usually no more than 72 hours. Other subforms are familial hemiplegic migraine types 1–3, sporadic hemiplegic migraine, and retinal migraine. Complications of migraine are status migrainosus (attack lasting more than 72 hours), persistent aura without infarction, migrainous infarction, and migraine aura-triggered seizure. Some episodic migraine patients develop chronic migraine, and high use of medication may play a role in chronicity. (Headache Classification Committee of the International Headache Society 2018, 18, 21–26; Jankovic et al. 2021, 294,251, 384; Ropper et al. 2019, 189.)

Table 1. Migraine without aura, migraine with aura, and chronic migraine: Diagnostic criteria (Adapted from Headache Classification Committee of the International Headache Society 2018, 19–20, 24)

Migraine without aura	**Migraine with aura**	**Chronic migraine**
At least five attacks fit the criteria below.	At least two attacks fit the criteria below.	Migraine or tension-type headache >15 days per month for at least three months.
Headache lasting 4–72 hours without treatment / with poor treatment effect.	At least one of the following (transient) aura symptom: visual, sensory, speech, motor, brainstem, or retinal symptom.	The patient has had at least five attacks of “migraine without aura” and/or “migraine with aura”.
Two or more characteristics: unilateral pain, pulsating type of pain, moderate or severe pain, physical activity provokes pain.	Three or more characteristics: one or more aura symptom occur over five minutes, two or more aura symptoms occur after each other, each aura symptom lasts 5–60 minutes, one or more aura symptoms are unilateral, one or more aura symptom is positive, headache appears after aura.	Minimum eight days per month, over three months: headaches that fulfill the criteria of “migraine without aura” and/or “migraine with aura”.
At least one symptom during headache: nausea, vomiting, photophobia, phonophobia.	No other ICHD-3 diagnosis is more appropriate.	No other ICHD-3 diagnosis is more appropriate.

No other ICHD-3 diagnosis is more appropriate.		

2.1.2 Epidemiology of Migraine

Second by low back pain, migraine is a worldwide leading cause of disability; within women in the 15–49 age group, it is ranked first. Migraine is the most prevalent neurological disorder and it has a significant financial impact on society. For example, in the United States, the annual cost of migraine is estimated to be 27 billion American dollars. Typically, first migraine attacks are experienced during adolescence or in early adulthood. (Ailani et al. 2021, 1022; Steiner et al. 2020, 1, 3; Jankovic et al. 2021, 248, 680.) During their lifetime, 17,6 % of people suffer from migraine. Lifetime prevalence is higher for women (21,0 %) than men (11,6 %). The monthly prevalence is 15,3 % for both genders (Stovner et al. 2022, 7). The highest prevalence is seen in 35–39-year-olds and the lowest within children and the elderly (Ashina et al. 2021, 1486). However, according to Finnish population-based studies, migraine incidence in children has been rising. In 1974, the incidence of migraine with aura was 5,2 / 1000-person years and without aura 14,5, respectively. In 2022, the same numbers were 41,3 and 91,9. (Anttila et al. 2006, 1200.)

Migraine is a hereditary disease, as 60–80 % of migraine with aura is inherited from one generation to another. Migraine without aura has a little lower percentage. Still, it is unclear how genetics lead to migraine presentation. Familiar hemiplegic migraine seems to be caused by variation in a single gene. Usually, patients experience their first attack before turning 30 years old. Although the number of migraine attacks decreases with age, attacks may turn out to be more frequent in some postmenopausal women. Sex hormones have multiple effects. Migraine tends to be relieved during the last two trimesters of pregnancy. Estrogen therapy might increase or opponently decrease the frequency of attacks. The use of birth control is associated with a higher number and higher intensity of attacks. (Ropper et al. 2019, 185, 188, 193.)

Different foods are thought to be triggering factors by many patients. These foods include good amounts of tyramine, e.g., cheese, chocolate, oranges, and tomatoes. However, this link has been disproved at a population level. Still, certain foods can trigger attacks in some patients. Alcohol can provoke attacks on some patients. Caffeine or sudden lack of caffeine is a typical provocateur. (Ropper et al. 2019, 188.)

Previously it was thought that there was a typical personality in migraine patients, including tenseness, perfectionism, and rigidity of thinking. However, there is no evidence of singular personality as a risk factor. Many patients associate stress and emotions with migraines, but again, these seem to be inconsequent. Migraine patients have a small rise in the incidence of seizures. Also, depressive and anxiety disorders are more common in migraine sufferers. Migraine has an association with increased stroke risk. (Jankovic et al. 2021, 985; Ropper et al. 2019, 189, 193.) Common vascular, neurological, psychiatric, and musculoskeletal comorbidities of migraine are listed in Table 2.

Table 2. Common comorbidities of migraine (Adapted from Burch et al. 2019, 637)

Vascular diseases	Myocardial infarction, stroke, Raynaud's phenomenon
Neurological diseases	Epilepsy, multiple sclerosis, restless legs syndrome, sleep disorders
Psychiatric diseases	Bipolar disorder, childhood adverse experiences, depression, generalized anxiety disorder, panic disorder, posttraumatic stress disorder
Musculoskeletal and pain diseases	Fibromyalgia, temporomandibular joint disorder
Other	Allergic rhinitis, asthma, systemic lupus erythematosus

Neck pain is more prevalent among migraine patients compared with the general population. Approximately 80 % of patients report neck pain simultaneously to migraine attacks, including prodromal and postdromal phases. Cervical range of motion, flexion-rotation test and forward head posture, and pain pressure threshold (on temporalis and sternocleidomastoid muscle) seem to be impaired in migraine patients. Also, temporomandibular disorder is more prevalent among migraine patients. The underlying mechanism is unclear. An anatomical connection between upper cervical nerves (C1–3) and trigeminal nerve (fifth cranial nerve) has been discovered, as their afferent signals have convergence. This mechanism can lead to perceived pain in another location and is a potential explanation for neck pain as a migraine symptom. Increased pain pressure threshold can be explained by hypersensitivity or allodynia, which are properties of hyperexcitable brain in migraine patients. (Ashina et al. 2015, 5; Bogduk 2001, 382; Gonçalves et al. 2011, 613; Jankovic et al. 2021, 1761; Lampl et al. 2015, 2; Szikszay et al. 2019, 563, 566–567.)

2.1.3 Causes of Migraine

There is no unequivocal theory to explain the cause of migraine. Previously, dilatation of arteries in the extracranial area, especially branches of the external carotid artery, was thought to be the reason for migraine and intracranial vasoconstriction cause of aura. However, functional MRI has shown that aura can take place without reduced blood flow, and during headaches blood flow can be reduced. During a migraine attack, vasodilatation of the superior temporal artery and middle cerebral arteries is documented; however, the attack can be present while blood flow is reduced. Commonly, patients having aura have reduced blood flow in the posterior cortical area. However, it is unclear whether blood flow changes are the important contributor or a consequence of decreased cortical activity. Although, there is still some evidence supporting this vascular theory as the cause of migraine, today's primary cause of migraine is considered to be related to alteration in normal brain function. Vascular changes might be secondary to these neural alterations. (Jankovic et al. 2021, 1759–1760; Ropper et al. 2019, 183, 193.)

Brain area responsible for migraine attacks is under debate; the hypothalamus and brainstem areas are possible migraine generators. It is not likely that one brain area is only responsible for migraine attacks; many areas of the brain are altered during the attack. Affected brain areas can be changeable from attack to attack even in the same patient; same as migraine symptoms can have variation in the same patient. The trigeminocervical system is an anatomical system that has an important role in migraine attacks. Trigeminal (fifth cranial nerve) and upper cervical nerves (C1–3) deliver afferent information from cranial and cervical areas to higher brain centers. Vasoactive neuropeptides, originating from sensory nerves innervating intracranial arteries, are released during activation of trigeminocervical system. This leads to so-called “neurogenic inflammation”, sensitization, and vasodilatation of arteries, which play a role in migraine headaches. Functional magnetic resonance imaging has shown that migraine patients have hyperexcitability and increased responses to sensory information. Recurrent activation of the trigeminocervical system can lead to changes in pain processing at peripheral and central levels. More than half of patients has allodynia during migraine attack which is a marker of central sensitization. The presence of central sensitization can reduce the effect of migraine medication. (Jankovic et al. 2021, 1759–1761; Ropper et al. 2019, 183, 185, 193–194.)

The underlying mechanism leading to aura is thought to be an electrophysiological phenomenon called “cortical depression spreading” (CDS), which starts in the occipital lobe and continues forward to the cerebral hemisphere. During CDS, a wave of cellular depolarization and repolarization takes part in the cortex. It is debated whether CDS lead to trigeminal activation leading to migraine attack. As migraine without aura -patients might not have CDS, other mechanisms for migraine attacks exist. (Jankovic et al. 2021, 1760.)

Migraine patients have brain imaging changes suggesting small ischemic lesions. Magnetic resonance imaging (MRI) has revealed deep and subcortical white matter changes especially in female migraine with aura patients in comparison to migraine patients without aura and non-migraine sufferers. The role of these findings is unknown (Jankovic et al. 2021, 985; Ropper et al. 2019, 185, 193). There has been a debate on the association with patent foramen ovale (a space between atriums in the heart), and especially migraine with aura. This association has not been confirmed and the theory is lately being forgotten. (Ropper et al. 2019, 193.)

2.1.4 Migraine Treatment

Migraine treatment focuses on the management of symptoms. Currently, there is no curable treatment. Patient education about migraine and its benign nature and prognosis is recommended. Treatment of acute migraine attacks aims for rapid relief of pain and restoration of function and relies mostly on medication. Many patients get relief using aspirin, paracetamol, or non-steroidal anti-inflammatory drugs (NSAID). Aspirin and paracetamol can be combined with caffeine. Treatment outcomes might differ between types of NSAIDs and a few different NSAIDs, one at a time, can be tested if needed. For more severe attacks, these medications might be inadequate and triptans are an effective choice. There are few different types of triptans, e.g., naratriptan, rizatriptan, zolmitriptan, almotriptan, eletriptan, and frovatriptan. A third of patients have insufficient treatment response with a triptan. If the treatment effect is poor with one triptan, another triptan can be effective. In addition to triptans, ergotamine tartrate, ergot alkaloids, and dihydroergotamine are effective. However, these medications should be used just when the attack begins, after a visual aura, or at the beginning of a headache. For patients who prefer non-medication treatment, transcutaneous electronic stimulation (TNS) of trigeminal nerve or upper limb nerves (remote electronic nerve stimulation, REN) might be an effective option. Behavioral therapies have limited effectiveness on acute migraine attacks. (Ailani et al. 2021, 1023, 1025, 1031; Daflög 2006, 104; Jankovic et al. 2021, 1761–1762; Ropper et al. 2019, 195.)

Lifestyle modifications and medication are the key preventative treatments to reduce migraine attacks. The treatment plan should be individualized. About 40 % of migraine patients (with or without aura) and almost every patient with chronic migraine would benefit from preventative treatment. Patients may need to avoid migraine-triggering factors, e.g., certain foods, alcohol, excessive caffeine intake, and stressors. Patients are recommended to have regular sleep and exercise routines. A quarter of migraine patients need medical treatment to prevent frequent migraine attacks. The pharmacological treatment plan should be followed for at least eight weeks to evaluate the treatment effect. First-line preventive drugs are beta-adrenergic blockers (e.g., propranolol and metoprolol), angiotensin receptor blockers (e.g., candesartan), antiepileptic drugs (e.g., topiramate) and antidepressants (e.g., amitriptyline). Calcium channel blockers (e.g., verapamil and flunarizine) have some effect. Propranolol might have a better effect on attack severity and amitriptyline on attack frequency. Previously mentioned medications have usually a good effect on attack frequency and severity. However, after several months, treatment tends to lose effectiveness. Increasing dosage or changing to alternative medicine might be needed. Injection therapies might play a role as a preventive treatment. Botulinum toxin injections to cranial muscles might have an effect for two to four months, however, more study is needed. Nerve blocks on the great occipital nerve (n. occipitalis major) have some effect. Non-pharmacological preventative treatments, such as acupuncture, meditation, biofeedback (electromyogram device to alert about myofascial tension as a marker of migraine attack), and relaxation therapies, are shown to be effective. Newer, potential treatment for attack prevention includes eptinezumab as an intravenous injection, electrical stimulation of the trigeminal nerve, and cognitive behavioral therapy. There is no evidence of the effectiveness of psychotherapy. (Ailani et al. 2021, 1023–1024, 1026, 1028, 1030, 1032; Jankovic et al. 2021, 1761, 1766; Ropper et al. 2019, 196–197.)

2.2 PHYSICAL ACTIVITY AND EXERCISE

Physical activity can be defined as “any bodily movement produced by skeletal muscles that requires energy expenditure” (World Health Organization 2022, 4). The benefits of regular exercise are well-documented. Being physically active is a necessary action for all ages to improve health and well-being. The Physical Activity Guidelines for Americans recommend at least 150 minutes of moderate-intensity aerobic exercise (e.g., walking 4–6,4 km per hour) or 75 minutes of vigorous-intensity aerobic exercise per week for adults (e.g., running). Muscle-strengthening exercises are recommended twice a week for adults. In older adults, the role of strength and balance training is crucial. During childhood, learning motor skills and exercise habits are important. Adolescents aged 6–17 is recommended to exercise three or more times a week in a vigorous-intensity and muscle-strengthening way. Youth who learn a physically active lifestyle are likely to have a healthier adulthood. To describe exercise intensity, using a scale from zero to ten can be used as one method. Moderate-intensity exercise is classified as five or six, and rigorous-intensity exercise as seven or eight or more out of ten. (Piercy et al. 2018, 3, 6, 8; World Health Organization 2022, 1.)

Endurance training can be classified as aerobic or anaerobic training, based on bioenergetics pathways responsible for adenosine triphosphate (ATP) production. Adenosine triphosphate-phosphocreatine (ATP-PC) and anaerobic glycolysis are energy pathways that don't require oxygen (O_2) to produce ATP and are called anaerobic energy pathways. ATP formation with O_2 is called aerobic metabolism. Small amounts of ATP are stored locally in muscles. During exercise, constant formation of ATP is necessary to create contraction in skeletal muscles. At the beginning of any exercise, ATP-PC is the first active metabolic pathway, followed by anaerobic glycolysis and aerobic energy pathways. During low-intensity training, the aerobic energy system mainly supplies energy for ATP production. During high-intensity training, energy is supplied by the ATP-PC system or glycolysis. In short-term high-intensity activity, lasting about 2–20 seconds, the ATP-PC system is mainly responsible for ATP production. From five seconds, anaerobic glycolysis starts and after 20 seconds it is the main energy system for ATP production. After 45 seconds of high-intensity activity, the aerobic energy system takes part and after 2 minutes, half of the energy is produced via aerobic and half via anaerobic energy systems. The main fuel for low-intensity exercise (maximum oxygen uptake, VO_2MAX 30 %) is fat and for high-intensity exercise (VO_2MAX 70 %) are carbohydrates. (Powers et al. 2020, 57–58, 79, 84, 90, 316.)

Resistance training (or strength training) is a type of exercise to increase muscle strength. Muscle strength increase is seen via training with heavy weights and short (for example from six to ten repetitions) sets, when energy is produced via anaerobic pathways. Muscle strength increase occurs via adaptations in the nervous system and an increase in muscle fiber cross-sectional size (called hypertrophy). In the first few months of training, adaptation occurs mostly via neural adaptations, which include an increase in the firing rate of motor neurons, the number of motor neurons activated, motor neuron synchronization, and neural transmission at the neuromuscular junction. When the training is continued for months, the role of muscle hypertrophy increases. (Powers et al. 84, 341, 345.)

Regular exercise has many health benefits. The benefits of exercise start cumulating immediately after physical activity. Acute effects of exercise are better mood, lower blood pressure, insulin function, and enhanced sleep. Long-term exercising leads to better cardiovascular function, increased muscle strength, and improvement in depressive symptoms (Piercy et al. 2018, 7). In addition, regular exercise improves cognitive function, reduces the risk of cardiovascular disease, prevents several types of cancer, and prevents falls. Following exercise recommendations leads to a 20–30 percent lower risk of premature death. Evidence supports “exercise as medicine” in the treatment of different long-term diseases, including psychiatric, neurological, metabolic, cardiovascular, pulmonary, and musculoskeletal diseases. (Luan et al. 2019, 433; Pedersen & Saltin 2015, 1; World Health Organization 2022, 1–2.)

Exercise is shown to be beneficial in the treatment of many musculoskeletal conditions, such as chronic low back pain, chronic neck pain, and osteoarthrosis (Gross et al. 2015, 34; Hayden et al. 2021, 20; National Institute for Health and Care Excellence 2022, 8). Exercise and physical activity are recommended treatments for many conditions. Based on specific conditions, general exercise or more specific (e.g., specific strengthening, mobility, coordination) prescription can be used. (Lin et al. 2021, 6.) In addition to musculoskeletal conditions, exercise interventions are beneficial in the treatment of primary headaches. A meta-analysis of aerobic exercise (mostly moderate-intensity aerobic exercise) clinical trials by Lemmens et al. (2019, 6) shows a positive effect on migraine days, leading to a 0,6 (+- 0,3) decrease in migraine days per month; nonpooled data suggests a small to moderate decrease on migraine attack pain intensity and duration. Based on a recent umbrella review by Varangot-Reille et al. (2022), craniocervical and upper limb strength training have a positive effect on tension-type headaches, however, strength of evidence was graded as limited. Aerobic exercise was found beneficial for migraine attack frequency (moderate evidence), headache duration (limited) and headache intensity (limited). However, overall effect indicates that the type of exercise might not have a great role in the outcome. (Lemmens et al. 2019, 6; Varangot-Reille et al. 2022, 4–5, 7.)

The effective mechanism behind exercise-induced hypoalgesia (EIH) in headaches is thought to be the release of endocannabinoids and beta-endorphin in descending inhibitory nociceptive pathways. Mechanisms via serotonergic, immune, or autonomic nervous system can play a role in EIH. Psychosocial factors (e.g., fear of movement or nocebo) might decrease EIH. Endurance exercise, especially at higher intensities (70 % of the maximum rate of oxygen consumption) is shown to lead to EIH. In addition to that, dynamic and isometric strength training is shown to lead to EIH. However, in some patients, exercise focused on local pain area might increase pain (implicating impaired EIH function) and exercise focusing on other body parts leads to normal pain decrease (implicating normal EIH function). In some patients, especially patients with higher pain sensitivity or widespread pain, all kinds of exercise might lead to more pain. (Goldfarb & Jamurtas 1997, 8–9; Rice et al. 2019, 1250, 1254–1255; Sparling et al. 2003, 2210; Varangot-Reille et al. 2022, 7.)

Physical inactivity is a rising concern worldwide and creates a burden for healthcare systems and the economy. In 2013, physical inactivity caused a global cost of 67,5 billion US dollars. Even though exercise significantly prevents noncommunicable diseases and improves health, physical inactivity is highly prevalent. Globally, over 25 % of adults and 80 % of adolescents do not follow physical activity guidelines. Physical inactivity is not evenly distributed; high-income countries have twice as high levels of physical inactivity compared to low-income countries. In most countries, boys and men are more active than girls and women. Older adults have a more passive lifestyle than younger adults. World Health Organization has a global target to achieve a 15 % reduction between 2018 and 2030; however, it seems to be unattainable without significant global effort. The actions of societies, environments, political systems, and individual people are urgently needed. (World Health Organization 2022, 1, 8, 10, 14.)

3 AIM, PURPOSE, AND RESEARCH QUESTION OF THE THESIS

This thesis aims to evaluate the effectiveness of exercise interventions for migraine in adult patients, using a systematized review method and content analysis. The purpose is to summarize information about the benefits of an exercise intervention to be helpful in education, clinical practice, and decision-making with migraine patients.

Research questions:

1. What is the effectiveness of exercise interventions compared to other interventions or control groups for…
    1.1. reducing attack frequency in adults with migraine with aura?
    1.2. reducing attack frequency in adults with migraine without aura?
    1.3. reducing attack frequency in adults with chronic migraine?
    1.4. reducing pain intensity during attacks in adults with migraine with aura?
    1.5. reducing pain intensity during attacks in adults with migraine without aura?
    1.6. reducing pain intensity during attacks in adults with chronic migraine?

The hypothesis was formed after the author was acquainted with the main concepts and previous research. The hypothesis of this thesis is that endurance and strength training exercise interventions have effectiveness on all included migraine patient groups, without the superiority of one exercise type.

4 METHOD

The method of this thesis was a systematized review, which is a suitable method for a master’s thesis and can be done by one student. Systematized review is inferior to a systematic review, but has the same elements and aims to systematical search and content analysis. (Grant & Booth 2009, 96, 103.) The project was documented carefully to ensure that replication is possible (Curtis & Drennan 2013, 133).

This thesis aimed to answer research questions by a systematized review process and content analysis, which is classified as a deductive research approach. Quantitative and objective methods are appropriate when evaluating treatment effectiveness in a specific population. As a randomized controlled trial (RCT) is recommended study design to evaluate single variables, e.g., treatment effectiveness, this thesis included only systematic reviews of RCT studies as appropriate to answer research questions. Qualitative studies were excluded as not suitable to answer research questions about treatment effectiveness. (Curtis & Drennan 2013, 133–134, 137, 140.) The study design is presented in Figure 1.

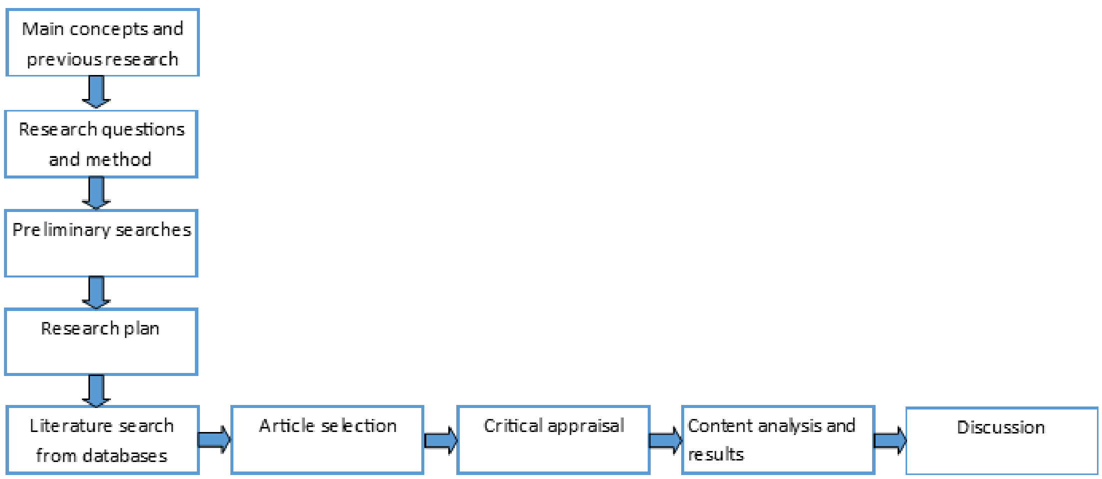

Figure 1. Study design

4.1 Data Collection

First, the author was acquainted with the main concepts and previous research before developing a search strategy. Research questions were formed using the PICO (population, intervention, comparison, outcome) framework (Higgings et al. 2022, section 2.3), see Table 3. Data was collected via a systematized database search process. Trial searches were completed with different search terms to form the final search terms. The search process, design, and terms were reported carefully. The final search terms and search results are documented in Table 5. An information specialist was consulted about the design of the search process. The search was done in multiple databases to minimize the risk of bias and not to miss relevant articles. (Higgins et al. 2022, section 4.1.1., 4.2.2, 4.4.2., 4.4.c.)

PubMed, SPORTDiscus, CINAHL, PEDro, and Web of Science databases were used. The selection of databases was thought carefully. PubMed, CINAHL, and Web of Science are widely used and comprehensive scientific databases in medicine and healthcare. SPORTDiscus and PEDro are relevant databases for this thesis as they focus on the exercise and rehabilitation research field.

Table 3. Research question in PICO (Patient, Intervention, Comparison, Outcome) framework

Patient	**Intervention**	**Comparison**	**Outcome**
Migraine patients	exercise	other interventions or control groups	migraine attack frequency, pain intensity during migraine attack

This thesis included systematic reviews of RCTs that have compared exercise interventions with other interventions or control groups in patients with migraine. Articles had to be written in English. Subjects had to be adults (over 18 years old) with migraine. Articles published between 1 January 2014 and 31 July 2023 in peer-reviewed journals were included to this thesis, see Appendix 1. Inclusion and exclusion criteria are listed in Table 4.

Inclusion criteria were slightly modified after the final search. In the research plan, patient age was defined as “18–65 years old”. After reviewing relevant articles, every relevant article defined adult as “18 years old or older”, so inclusion criteria in this thesis were modified accordingly. In addition to that, the research plan defined included migraine type as “migraine with aura, migraine without aura or chronic migraine” and exclusion criteria was “Qualitative studies and studies done on children or other migraine classification patients as subjects will be excluded”. After reviewing relevant systematic reviews, there were no articles suitable for these criteria articles included “migraine” or “episodic migraine” patients, so again, the inclusion criteria in this thesis were modified.

Table 4. Inclusion and exclusion criteria in this thesis

Inclusion criteria	**Exclusion criteria**
Systematic reviews of randomized controlled trials, comparing exercise interventions among other intervention or control group	Studies that have been done on children
Subjects are adults (18 years old or older) with migraine	Qualitative research studies
Written in English	
Published between 1 January 2014 and 31 July 2023 in peer-reviewed journal	

During August and September 2023, trial searches were conducted to create an overall picture of available studies. During trial searches, different search terms and combinations were tested in every database. Boolean operators were used. Subject Headings were used in CINAHL (“migraine”, “exercise”) and PubMed (“migraine disorders”, “exercise”) databases. Trial searches began with search terms “exercise” and “migraine”. The search was supplemented with relevant keywords, as "physical activity", “training”, and "migraine headache". The final search term included “systematic review”, which helped to narrow results without missing relevant articles.

The final search was done on 18 September 2023. Search terms were: *(exercise OR "physical activity" OR training) AND (migraine OR "migraine disorders" OR "migraine headache") AND “systematic review” AND 2014/01/01:2023/07/31[dp]* in PubMed; *(exercise OR "physical activity" OR training) AND (migraine OR "migraine disorders" OR "migraine headache") AND “systematic review”* in SPORTDiscus, CINAHL and Web of science; and *migraine exercise* in PEDro. The search resulted in overall 215 results. Search terms and results are presented in Table 5.

Database-specific search filters were used as follows: in Pubmed, the “English” language filter was selected. In SPORTDiscus and CINAHL, “apply equivalent subjects”, “peer-reviewed” and “English” filters were selected. All databases, except PEDro, were allowed to set the publication date by dd/mm/yyyy, which is in this thesis 01/01/2014–31/07/2023. PEDro has only “published since” filter, “2014” was selected there.

Table 5. Search terms in this thesis

Database	**Search term**	**Number of results**
PubMed	(exercise OR "physical activity" OR training) AND (migraine OR "migraine disorders" OR "migraine headache") AND “systematic review” AND 2014/01/01:2023/07/31[dp]	97
SPORTDiscus	(exercise OR "physical activity" OR training) AND (migraine OR "migraine disorders" OR "migraine headache") AND “systematic review”	9
CINAHL	(exercise OR "physical activity" OR training) AND (migraine OR "migraine disorders" OR "migraine headache") AND “systematic review”	15
PEDro	migraine exercise	27
Web of Science	(exercise OR "physical activity" OR training) AND (migraine OR "migraine disorders" OR "migraine headache") AND “systematic review”	67
Overall		215

4.2 Analysis

After a final search, duplicates (N=62) of the same study were removed. Articles were screened by reading title and abstract to include potentially relevant articles that might fill the inclusion criteria requirements (N=15). If the inclusion decision could not be made only by title and abstract, the full text was read (N=15). Reasons for exclusion were documented (overall N=12; wrong setting N=5, wrong intervention N=1, wrong study design N=3, not written in English N=1, wrong patient population N=1) and excluded articles are listed in Appendix 6. The screening was done using Covidence software, which is “a web-based collaboration software platform that streamlines the production of systematic and other literature reviews” (Covidence systematic review software, n.d.). The quality of included systematic reviews was assessed using the critical appraisal tool “A Measurement Tool to Assess Systematic Reviews 2” (AMSTAR 2). Based on AMSTAR 2, study quality was rated as high, moderate, low, or critically low (Shea et al. 2017), see Table 6. The appraisal process was essential to evaluate study quality and recognize major methodological flaws. (Boland et al. 2017, 341.) Characteristics of included studies and critical appraisal results were documented.

Table 6. AMSTAR 2 study quality rating (Shea et al. 2017, 6)

Study quality	Description
High	No or one non-critical weakness
Moderate	More than one non-critical weakness
Low quality	One critical flaw with or without non-critical weaknesses
Critically low	More than one critical flaw with or without non-critical weaknesses

Three articles were included in this thesis (see flowchart in Appendix 2.) Included articles were reviewed for relevance to research questions and divided into groups. Groups were divided by research questions: “Exercise and attack frequency” and “Exercise and pain intensity”. Findings related to study design, participants, intervention, and outcomes were summarized in the report and were presented in tables. Only data relevant to the research questions were reported. (Higgins et al. 2022, 5.3.a; 5.5.6.)

5 RESULTS

5.1 Study Characteristics

This systematized review consists of three systematic reviews of randomized controlled studies. Each systematic review additionally incorporated a meta-analysis. Included studies aimed to evaluate the effectiveness of exercise interventions on migraine. Aerobic exercise was the most studied exercise intervention in RCTs within the systematic reviews, see Table 7. Aerobic exercise was carried out three times a week in most studies, one session lasting between 40–60 minutes. See the comprehensive study characteristics in Appendix 3 and the characteristics of RCTs in included systematic reviews in Appendix 5.

Table 7. Exercise interventions in RCTs included in systematic reviews

Exercise intervention	Number of studies (authors)
Aerobic exercise	Eight studies, five investigated moderate-intensity training, one combined 15 min relaxation to moderate-intensity training, one investigated aerobic and relaxation training (two study groups), and one investigated high-intensity and moderate-intensity training (two study groups) (Darabaneanu et al. 2011, Dittrich et al. 2008, Hanssen et al. 2018, Krøll et al. 2018, Narin et al. 2003, Oliveira et al. 2019, Santiago et al. 2014, Varkey et al. 2011).
Multidisciplinary treatment	Two studies (Gunreben-Stempfle et al. 2009, Lemstra et al. 2002) Gunreben-Stempfle et al. intervention included cognitive behavioral therapy, patient education, biofeedback therapy, aerobic exercise, strength, and relaxation training; Lemstra et al. intervention included aerobic, strength, and relaxation training, dietary lectures, massage therapy.

After careful screening and study selection, it appeared that there was no existing systematic review of randomized controlled trials with separate analyses for exercise effectiveness on chronic migraine, migraine with aura, and migraine without aura. Two included systematic reviews had inclusion criteria for RCTs on “adults with migraine” (Beier et al. 2022; Luedtke et al. 2016) and one for “episodic migraine” (Pi et al. 2022), meaning that RCTs on participants with all types of migraine were included in two reviews and chronic migraine was excluded on one review. Based on current literature, research questions cannot be answered by focusing on one migraine subform at a time, so in this thesis, effectiveness on migraine attack intensity and migraine attack frequency was reviewed on all migraine patients without subforms.

Study quality appraisal was conducted with the AMSTAR 2 tool. Apprehensive AMSTAR 2 quality ratings are shown in Appendix 4 and summary in Table 8. One systematic review (Beier et al. 2022) was classified as high-quality and two as low-quality studies. Beier et al. (2022) scored “no” only in one section: “Did the review authors report on the sources of funding for the appropriate methods for statistical combination of results?”. Luedtke et al. (2016) scored “no” in the sections: “Did the review authors perform data extraction in duplicate?”, “Did the review authors provide a list of excluded studies and justify the exclusions?” and “Did the review authors report on the sources of funding for the studies included in the review?”, resulting in low-quality study. Pi et al. (2022) scored “no” in the same sections, except “yes” in “Did the review authors perform data extraction in duplicate?”, resulting in also low-quality study.

Table 8. Study quality of included studies

Study	**Study quality (AMSTAR 2)**
Beier et al. 2022	High
Luedtke et al. 2016	Low
Pi et al. 2022	Low

Impact factor (IF) is often used to evaluate the importance of scientific journals. IF measures how often an average article in the journal is cited. An impact factor of 1,0 indicated an average number of citations. (Boland et al. 2017, 368.) Included studies were published in *Cephalgia* (IF 4,9) and *Medicine* (IF 1,817) (Ovid Technologies, n.d.; Sage Publications, n.d.), see Table 9.

Table 9. 2023 Impact Factor of journals where articles were published in (authors of the included article)

Journal	**Impact factor (IF)**
Cephalgia (Beier et al. 2022; Luedtke et al. 2016)	4,9
Medicine (Pi et al. 2022)	1,817

Beier et al. (2022) aimed to update guidelines and evaluate the effectiveness of non-pharmacological treatment options for migraine. This systematic review included six RCT studies: two investigated aerobic and relaxation exercises, one moderate-intensity and high-intensity exercise, and two aerobic exercises and one combined aerobic exercise and medication (amitriptyline). Participant numbers in the included RCTs were 30, 48, 50, 52, 60, and 91. Evidence was graded as very low-quality (GRADE assessment). The risk of bias was high. This review included three same RCTs as Pi et al. (2022) and one similar with Luedtke et al. (2016). In the meta-analysis, the authors used mean difference (MD) for continuous outcomes and when different measurement scales were used in studies, standardized mean difference (SMD) was used to estimate effect size. Confidence intervals (95 %) were calculated.

Luedtke et al. (2016) aimed to evaluate the effectiveness of interventions delivered by physiotherapists on migraine headaches, tension-type headaches, and cervicogenic headaches. This systematic review included only RCT and cross-over (data only from the first phase before the switch) studies in which intervention were delivered by physiotherapists. The qualitative synthesis included 26 studies and the quantitative (meta-analysis) 20 studies. This systematic review included 26 RCT studies, of which six investigated exercise interventions on migraine patients:, four studies investigated aerobic exercises (Dittrich et al. 2008 included 15 min of relaxation to exercise; Varkey et al. 2011 had also a relaxation training group), one combined training (including aerobic, strength, and relaxation), and one multidisciplinary treatment (including individual and group therapy, including cognitive behavioral therapy, patient education, biofeedback therapy, aerobic exercise, strength and relaxation training). Participant numbers in the included exercise RCTs were 16, 30, 40, 61, 77, and 80. Evidence was graded as low-quality (GRADE assessment). The risk of bias included many “unclear” and “high” ratings. This review included two same RCTs as Beier et al. (2022) and one similar as Pi et al. (2022). In the meta-analysis, the authors used mean difference and confidence intervals (95 %) to estimate effect size.

Pi et al. (2022) aimed to evaluate the effects of neuromodulation, acupuncture, and aerobic exercises in patients with episodic migraine and tension-type headaches. This systematic review included 27 RCT studies, of which three were studies investigating aerobic exercise in patients with episodic migraine. Participant numbers in the included exercise RCTs were 52, 48, and 91. Evidence was graded as low-quality (GRADE assessment). The risk of bias was moderate. This review included three same RCTs as Beier et al. (2022) and one similar as Luedtke et al. (2016). In the meta-analysis, authors used weighted mean difference and confidence intervals (95 %) to estimate effect size.

Authors of all systematic reviews used GRADE (Grading of Recommendations Assessment, Development, and Evaluation) to assess the certainty of evidence and the Cochrane Risk of Bias tool to assess the risk of bias. Luedtke et al. (2016) and Pi et al. (2022) stated the following of guidelines based on the Cochrane Handbook for Systematic Reviews and reporting on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements. All authors used I^2 statistics to assess heterogeneity in studies. All three systematic reviews state no conflicts of interests. (Beier et al. 2022, 64, 67, 71; Luedtke et al. 2016, 477, 490; Pi et al. 2022, 1, 3.)

5.2 Effectiveness of Exercise Interventions on Migraine Attack Intensity

Beier et al. (2022, supplementary figure 3) included two aerobic exercise RCTs in their meta-analysis on migraine attack intensity, which were conducted by Krøll et al. (2018) and Varkey et al. (2011). The meta-analysis found that supervised exercise interventions had no statistically significant effect on migraine attack intensity after treatment (standardized mean difference, SMD 0,69 [0,29; 1,10]). High heterogeneity was present (I^2 = 98 %).

Luedtke et al. (2016, 484) included five exercise RCTs (three on aerobic exercise, multidisciplinary program, and combined aerobic, strength, and relaxation training) in their meta-analysis on migraine attack intensity, conducted by Darabaneanu et al. (2011), Gunreben-Stempfle et al. (2009), Lemstra et al. (2002), Narin et al. (2003), Varkey et al. (2011). Three of the studies had a high risk of bias. The meta-analysis found no statistically significant effect on migraine attack intensity (mean difference, MD -0,62 [-2,89; 1,65]). However, in a separate analysis, studies with a low risk of bias, Lemstra et al. (2002, aerobic, strength, and relaxation training compared to waiting list) and Narin et al. (2003, aerobic exercise compared to no intervention) showed statistically significant effects favoring intervention group, MD -1,94 [-2,61; -1,27] and -3,00 [-3,73; - 2,27], respectively. High heterogeneity was present (I^2 = 98 %).

Pi et al. (2022, 10) included two aerobic exercise RCTs in their meta-analysis on migraine attack intensity, conducted by Krøll et al. (2018) and Varkey et al. (2011). Authors included studies on neuromodulation and acupuncture in the same meta-analysis, so an overall analysis of exercise interventions is not available. In a separate analysis of the study by Krøll et al. (2018), statistical significance was found favoring the control group (WMD 1,60 [0,46; 2,74]). Varkey et al. (2011) did not reach statistical significance (WMD 0,90 [-0,03; 1,83]). Heterogeneity was not reported separately for exercise RCTs.

These findings indicate no clear evidence on the effectiveness of exercise interventions on migraine attack intensity, so the hypothesis was disproved. Two RCTs with low risk of bias, Lemstra et al. (2002) and Narin et al. (2003) showed a statistically significant decrease in migraine attack intensity (Pi et al. 2022, 10). The authors stated the quality of included RCTs as low- to very low-quality.

No adverse effects were reported in the included studies.

5.3 Effectiveness of Exercise Interventions on Migraine Attack Frequency

Beier et al. (2022, supplementary figure 3) included three aerobic exercise RCTs in their meta-analysis on migraine attack frequency, conducted by Krøll et al. (2018), Santiago et al. (2014), and Varkey et al. (2011). The meta-analysis found that supervised exercise interventions had no statistically significant effect on migraine attack frequency after treatment (SMD -0,86 [-1,81; 0,09]) or after follow-up (SMD -0,21 [-0,75; 0,32]). High heterogeneity was present (I^2 = 98 % and 50 %). However, in a separate analysis, Santiago et al. (2014, amitriptyline and exercise compared to amitriptyline) and Varkey et al. (2011, aerobic exercise group and relaxation exercise group compared to daily topiramate) reached statistically significant effect favoring exercise groups after treatment, SMD -1,62 [-2,26; -0,97] and -1,06 [-1,60; -0,52], respectively.

Luedtke et al. (2016, 484) included five exercise RCTs (three on aerobic exercise, multidisciplinary program, and combined aerobic, strength, and relaxation training) in their meta-analysis on migraine attack frequency, conducted by Darabaneanu et al. (2011), Gunreben-Stempfle et al. (2009), Lemstra et al. (2022)., Narin et al. (2003) and Varkey et al. (2011). The meta-analysis found no statistically significant effect on migraine attack frequency (MD -2,99 [-7,85; 1,87]. In separate analyses (studies with low risk of bias) Lemstra et al. (2002), Narin et al. (2002) and Varkey et al. (2011) found statistically significant effects favoring the intervention group, MD -9,07 [-9,52; -8,62], -3,40 [-4,66; -2,14] and -0,35 [-0,62; -0,08], respectively. High heterogeneity was present (I^2 = 100 %).

Pi et al. (2022, 10) included three exercise RCTs (one with high-intensity exercise and moderate aerobic exercise groups, two aerobic exercises) in their meta-analysis on migraine attack frequency, conducted by Hanssen et al. (2018), Krøll et al. (2018) and Varkey et al. (2011). Authors included studies on neuromodulation and acupuncture in the same meta-analysis, so combined analysis on only exercise interventions is not available. In a separate analysis, exercise interventions did not reach statistically significant effects, (WMD -0,60 [-

1,72; 0,52], 0,0 [-2,61; 2,61] and -1,36 [-2,88; 0,16]. Heterogeneity was not reported separately for exercise RCTs.

These findings indicate no clear evidence of the effectiveness of exercise interventions on migraine attack frequency, so the hypothesis was disproved. However, three individual RCTs, Lemstra et al. (2002), Narin et al. (2003), and Varkey et al. (2011) showed a statistically significant reduction in migraine attack frequency (Luedtke et al. 2016, 484). Mainly, the quality of included RCTs was low to very low.

No adverse effects were reported in the included studies.

6 DISCUSSION

6.1 Discussing the Results

This thesis aimed to review literature via a systematized review process to answer research questions. The thesis consisted of three systematic reviews of randomized controlled trials. After data search and screening, it was noticed that separate analysis on different migraine subforms was not possible with current systematic reviews, so this thesis summarised results with migraine patients as one group. Pi et al (2022) included only RCTs investigating patients with "episodic migraine", two other systematic reviews included RCTs investigating all "migraine patients". These reviews overlapped with the same studies, so comparing the effectiveness of exercise on episodic and chronic migraine patients was not possible.

The results of this thesis indicated no statistically significant evidence of exercise effectiveness on migraine attack intensity and frequency. Nonetheless, most RCTs in included systematic reviews were small, methodologically low quality, including different headache types, different interventions, and reporting non-unified outcomes. In the future, high-quality RCT studies with larger study groups, better methodological quality, and more comparability are needed to give more accurate answers on effectiveness of exercise interventions on migraine attack intensity and frequency. High heterogeneity in methods and interventions has an impact on generalizability. (Beier et al. 2022, 70, supplementary figure 3; Luedtke et al. 2016, 489–490; Pi et al. 2022, 12.) Inclusion criteria in RCTs were variable according to migraine subform (see Appendix 5.). The included studies did not use any individualization on intervention, for example, individual response to exercise modality. Neither, if exercise type or intensity was a migraine trigger, it was not noted. Luedtke et al. (2016, 489) discussed that maybe with individualized treatments, effectiveness could be more significant.

The results were not as hypothesized, as the effectiveness of exercise interventions was not statistically significant. However, few RCTs provide promising findings on the possible effectiveness of exercise on migraine intensity and attack frequency. Separate analysis on Lemstra et al. (2002) and Narin et al. (2003) showed statistically significant effectiveness on both migraine intensity and frequency and Varkey et al. (2011) on migraine frequency (Luedtke et al. 2016, 484). These RCTs had a low risk of bias, which increases their weight and clinical significance. However, it should be noted that Lemstra et al. (2002) included non-exercise interventions, such as massage and nutrition lectures; it is not possible to know which part of the intervention was the most effective one.

When evaluating treatment effectiveness, in addition to statistical significance, clinical significance should be considered. The statistically significant result might have only a little clinical significance if the treatment effect is too small (Curtis & Drennan 2013, 25). Pi et al. (2022, 12) point out that usage of the weighted mean difference (WMD) does not directly translate their results into clinical significance. Luedtke et al. (2016, 489) point out that many of the effects were clinically small; Gunreben-Stempfle et al. (2009) intensive multidisciplinary program led reduction of pain only effect of –0,80 on a 0–10 VAS. There is no standard for clinically meaningful differences in headache populations (Luedtke et al. 2016). For example, in low back pain studies, a reduction of 2,4 is considered clinically significant (Maughan & Lewis 2010,1940). In the included studies, the observed effects appear to be modest at best and may not have practical implications in real-life scenarios.

6.2 Other Perspectives on Exercise and Migraine

The research questions of this thesis focused on migraine attack intensity and frequency as outcomes. There are other outcomes to determine the benefits of exercise on migraine symptoms. In the included studies, Beier et al (2022, 69) found that exercise might have a positive effect on quality of life, based on a study by Varkey et al. (2011). Luedtke et al. (2016, 484–485) found a reduction of migraine attack duration after aerobic exercise and physical exercise with combined psychological intervention, based on studies by Lemstra et al. (2002, chronic migraine patients) and Narin et al. (2003, migraine without aura). These findings support exercise routines as part of migraine treatment.

This systematized review included only systematic reviews of randomized controlled trials. This decision was made as the RCT study method is the golden standard method for evaluating treatment effectiveness (see 4 Method). However, a wider inclusion criterion, including other experimental and observational studies, might have an impact on results. For example, one excluded study was a recent systematic review and network meta-analysis, which included non-randomized studies, found the highest reduction in monthly migraines with strength training intervention (low to very low quality of evidence). The second and third highest reduction was reported with high-intensity and moderate-intensity aerobic exercise. The authors speculate that the possible effect of strength training takes place via its positive effects on the neck, reducing input on the trigeminocervical system. The superiority of strength training and high-intensity aerobic training might be explained by more significant exercise-induced hypoalgesia at higher intensities (See 2.2. Physical activity and exercise). However, this systematic review has received critique on multiple methodological considerations that can alter outcomes. (Han & Cho 2022, 1–2; Woldeamanuel & Oliveira 2022, 5, 7.)

In this thesis, one RCT by Hanssen et al. (2018), included in two systematic reviews (Beier et al. 2022; Pi et al. 2022), found that high-intensity exercise, 4 x 4 min at 90–95 % at maximum heart rate, was superior to moderate-intensity exercise, 70 % of maximum heart rate, on migraine day reduction, supporting this superiority. Most included RCTs in systematic reviews in this thesis investigated moderate aerobic exercise; only two investigated other interventions. Most often intervention was compared to no training (Appendix 5.). In the future, more research on high-intensity training or strength training effectiveness on migraine and research comparing the effectiveness of different exercise types on migraine would be interesting to see, if the superiority of strength training and high-intensity training could be consistently replicated.

Another systematic review and meta-analysis on the effectiveness of aerobic exercise on migraine, which was excluded for including non-randomized studies, found a statistically significant reduction in migraine pain intensity, duration and frequency, based on low to moderate quality evidence. (La Touche et al. 2019, 973, 976.) A systematic review and meta-analysis by Lemmens et al. (2019, 6), which was excluded for the same reason, found statistical significance in the reduction of the number of migraine days (moderate quality evidence). However, clinical significance was small (mean reduction of 0.6 ± 0.3 migraine days per month). These systematic reviews included many same RCTs as systematic reviews in this thesis; results of non-randomized studies or differences in study methods might explain differences in findings in different systematic reviews. In addition to systematic reviews, observational studies support exercise and physical activity as part of migraine treatment. Low levels of activity are associated with a higher prevalence of migraine. (Dominques et al. 2011, 41; Molarius et al. 2008, 1431; Varkey et al. 2008, 1295.) These findings support exercise routines as a nonpharmacological part of migraine treatment.

Physical activity and exercise have many well-documented benefits (See 2.2 Physical activity and exercise), including exercise-induced hypoalgesia. Every adult, including migraine patients, should follow physical activity guidelines and regularly practice endurance and muscle-strengthening exercises. Most of the RCTs in included the systematic review focused only on one intervention, mainly moderate aerobic exercise (See Appendix 5.). Two RCTs investigated the idea of combined training as an effective treatment for migraine patients. Gunreben-Stempfle et al. (2009, multidisciplinary treatment including cognitive behavioral therapy, biofeedback, aerobic, strength and relaxation training) and Lemstra et al. (2002, aerobic, strength and relaxation training, dietary lecture, massage therapy) studied multimodal treatment. In their study reports, both study groups state statistically significant improvements in the study group. These results might indicate that education and advice to exercise according to physical activity guidelines might be simple nonpharmacological treatment options for migraine patients.

6.3 Credibility, Strengths, Weaknesses, and Ethics of the Thesis

Reliability is defined as the capability to give the same measurement in different measurement sessions (Boland et al. 2017, 315). To improve the reliability of this thesis, the author familiarized himself with review and search processes. The study design decision was informed by a review of the relevant literature on research methods. The reliability of the study was enhanced through a thoughtfully formed search strategy. Only peer-reviewed literature was included in this thesis. A systematized review should be repeatable and updateable, so the process of this thesis was documented carefully. Internal and external validity are important to consider when conducting and evaluating research. Internal validity refers to the accuracy of the study and the accuracy of the study results, and how the research measures what it was intended to measure. External validity means the generalizability of research results, in other words, whether conclusions can be drawn from the results to other populations. (Curtis & Drennan 2013, 133, 136, 140; Grant & Booth 2009, 103.) Familiarization with the research methods, regular consultation with supervisors, and careful attention to detail at every phase contribute to enhancing the internal validity of this thesis. The external validity and generalizability of results are compromised by methodologically weak and small-scale RCTs in included systematic reviews.

This thesis has many strengths. Every phase of the thesis process was reported carefully. Theoretical framework and main concepts were defined with a review of the recent literature. Methodological choices and inclusion criteria were valid and suitable to answer research questions; systematic reviews facilitate comprehensive coverage of existing RCT research in the field, as RCTs are considered the optimal method for assessing treatment effectiveness. The search strategy was formed with several test searches. Database search was wide as many relevant databases were selected. Article screening was done systematically with Covidence, which is a specially designed software for the purpose. The process maintained a clear focus throughout, resulting in coherent completion of the thesis without diverting the focus outside the topic.

This thesis has several weaknesses, too. Research questions were formulated to answer the effectiveness of exercise interventions on migraine frequency and intensity separately in patients with migraine with aura, migraine without aura, and chronic migraine. However, current systematic reviews of RCTs included migraine patients without subforms defined in research questions. During the background and study planning phases, the author could have acquainted themselves better with the contemporary systematic reviews and the respective patient populations therein. This discrepancy was remedied by presenting the results based on the existing patient populations within the RCTs in the systematic reviews.

Another weakness is only one author in this thesis, who was implementing the systematized literature method for the first time. Compared to funded projects by research teams like systematic reviews, this thesis was done only by one master’s student with limited knowledge and experience in methodology, statistics, and conducting research, resulting in a higher risk of bias. To mitigate this potential bias, the assistance of supervisors and the guidance of information specialist were sought to enhance methodological quality and overall research conduct.

Ethical aspects were considered following the Guidelines of the Finnish National Board on Research Integrity (2023). According to The European Code of Conduct for Research Integrity (2017, 4), good research practice includes reliability, sincerity, respect, and liability. The publications of others were referenced appropriately. The thesis was carried out objectively and without distorting the results. Copyright legislation was respected when using databases and retrieving articles. (Finnish Research Ethics Advisory Board Guideline 2023, 11, 14; Higgins et al. 2022, Section 4.2.4.)

6.4 Conclusion

The results of this thesis should be taken with caution because of methodological considerations. Two of the three included systematic reviews (Luedtke et al. 2016; Pi et al. 2022) were rated (AMSTAR 2) as low-quality studies. (See Appendix 4.) Luedtke et al. (2016) did not report data extraction done in duplication, which decreases the reliability of study (Higgins et al. 2022, section 5.5.2). None of the studies reported funding of included RCTs and provided a list of excluded studies and exclusion reasons, which has a potential impact on study reliability. In addition to that, RCTs in systematic reviews were mainly small studies with low methodological quality. (Beier et al. 2022, 70; Luedtke et al. 2016, 489–490; Pi et al. 2022, 12.) These methodological issues should be noted when making generalizations based on this thesis. It should be noted that two of the included systematic reviews (Beier et al. 2022; Luedtke et al. 2016) were published in journals with moderately high impact factors (4,9; *Cephalgia*) and third (Pi et al. 2022) in journals with slightly above than average impact factor (1,817; *Medicine*); both journals are peer-reviewed. (Clarivate 2023, 18.)

To summarize, the cornerstone treatment of acute and preventive treatment of migraine is patient education and medical treatment. The results of this thesis indicate that aerobic exercise might be a beneficial option for additional nonpharmacological treatment. While some evidence points out that exercise can trigger migraine attacks (Amin et al. 2018, 3), exercise was shown not to have serious adverse effects in the included studies. Every adult, migraine sufferer or not, should follow physical activity guidelines to improve health and well-being. In the future, high-quality randomized controlled studies are needed on the topic.

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LIST OF TABLES

Appendix 1/1

Migraine Classification according to International Classification (2018, 18)

1. Migraine
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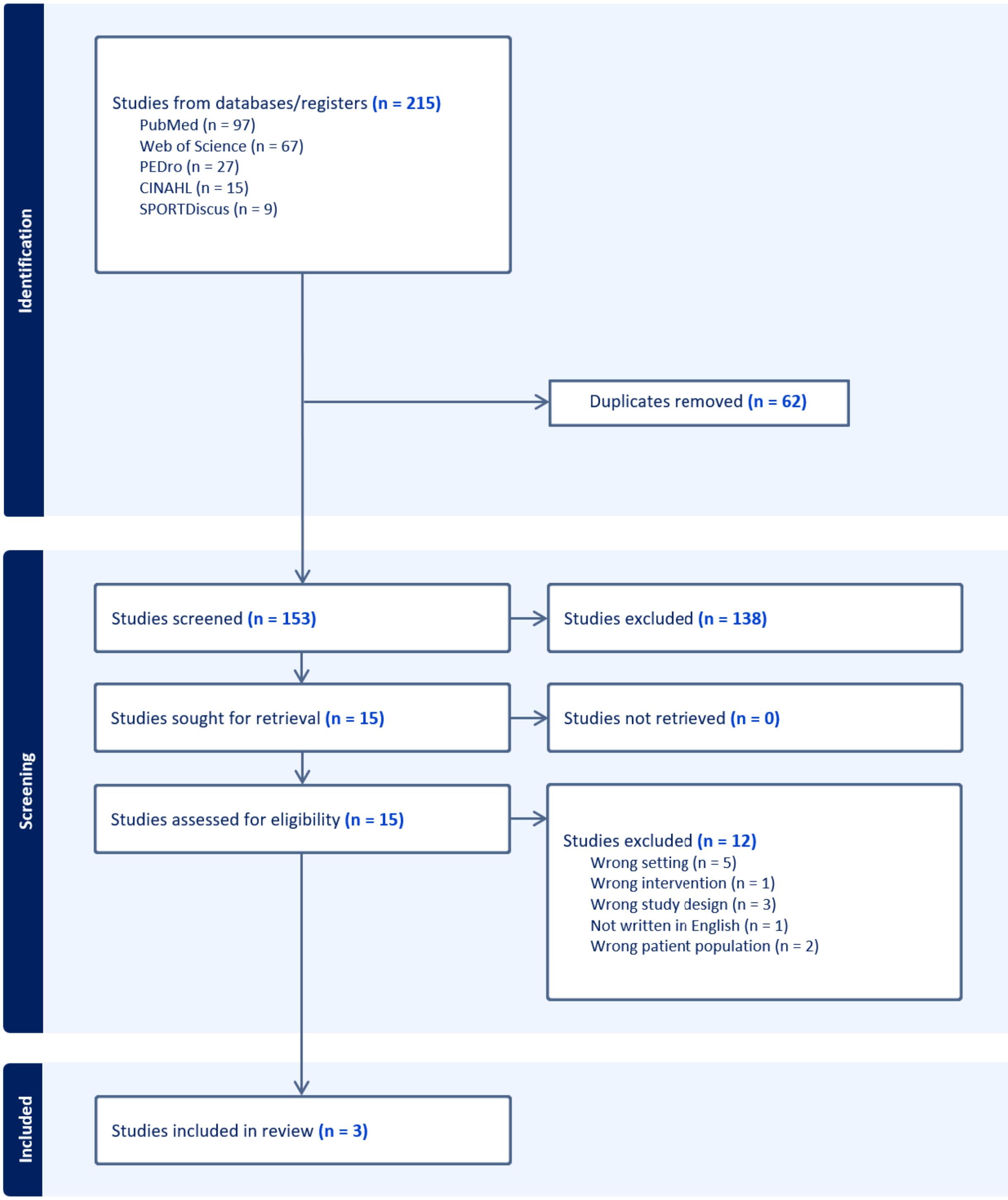
    1.2. Migraine with aura
        1.2.1. Migraine with typical aura
            1.2.1.1. Typical aura with headache
            1.2.1.2. Typical aura without headache
        1.2.2. Migraine with brainstem aura
        1.2.3. Hemiplegic migraine
            1.2.3.1. Familial hemiplegic migraine (FHM)
                1.2.3.1.1. Familial hemiplegic migraine type 1 (FHM1)
                1.2.3.1.2. Familial hemiplegic migraine type 2 (FHM2)
                1.2.3.1.3. Familial hemiplegic migraine type 3 (FHM3)
                1.2.3.1.4. Familial hemiplegic migraine, other loci
            1.2.3.2. Sporadic hemiplegic migraine (SHM)
        1.2.4. Retinal migraine
    1.3. Chronic migraine
    1.4. Complications of migraine
        1.4.1. Status migrainosus
        1.4.2. Persistent aura without infarction
        1.4.3. Migrainous infarction
        1.4.4. Migraine aura-triggered seizure
    1.5. Probable migraine
        1.5.1. Probable migraine without aura
        1.5.2. Probable migraine with aura
    1.6. Episodic syndromes that may be associated with migraine
        1.6.1. Recurrent gastrointestinal disturbance

1.6.1.1 Cyclical vomiting syndrome
1.6.1.2 Abdominal migraine
1.6.2 Benign paroxysmal vertigo
1.6.3 Benign paroxysmal torticollis

Prisma Flow Chart



The Study Characteristics of the Included Systematic Reviews

Study	Study authors, place of study, year, journal (Impact factor)	Purpose of the study	Participants and list of exercise interventional RCTs	Data collection and analysis method	Main results (with focus on research questions of this thesis)
Manual joint mobilization techniques, supervised physical activity, psychological treatment, acupuncture and patient education in migraine treatment. A systematic review and meta-analysis.	Beier, D., Callesen, H. E., Carlsen, L. N., Birkefoss, K., Tómasdóttir, H., Wűrtzen, H., Christensen, H. W., Krøll, L. S., Jensen, M., Høst, C. V., & Hansen, J. M. Denmark. 2022. Cephalgia (IF 4,9).	”To provide an updated guideline for some widely used non-pharmacological treatment options for migraine”. There were well defined PICO questions for every studied intervention.	Adults with migraine. Included six exercise RCTs (intervention at least 6 weeks): two investigated aerobic and relaxation exercise, one moderate and high intensity exercise, and two aerobic exercise, combined one aerobic exercise and medication (amitriptyline) - Dittrich et al. 2008 - Hanssen et al. 2018 - Krøll et al. 2018 - Oliveira et al. 2019 - Santiago et al. 2014 - Varkey et al. 2011	Systematic review of randomized controlled studies that tested effectiveness of manual joint mobilization techniques, supervised physical activity, psychological treatment, acupuncture or patient education in migraine treatment. Database search: EMBASE, MEDLINE, PsycINFO, CINAHL, PEDro. Cochrane Risk of Bias tool was used. Meta-analysis was conducted. I2 statistics was used for heterogeneity. Weighted mean difference was calculated. Patient preference was evaluated via questionnaire focusing on patient expectations on different treatments. GRADE approach was used for making recommendations.	Main results were: 1) Supervised physical activity might be effective for quality of life (very low evidence, because of risk of bias, inconsistency and imprecision); 2) Manual therapy and psychological treatment had no effect; 3) Patient education might have an effect on patient knowledge, quality of life and self-rated health. Notice: Heterogeneity on most treatments, lack of standardization in studies. Evidence certainty for all included studies was low to very low (GRADE).

Efficacy of interventions used by physiotherapists for patients with headache and migraine—systematic review and meta-analysis.	Luedtke, K., Allers, A., Schulte, L. H., & May, A. 2016. Germany. Medicine (IF 1.817).	"To conduct a systematic review evaluating the effectiveness of interventions used by physiotherapists on the intensity, frequency and duration of migraine, tension-type (TTH) and cervicogenic headache (CGH)." There was well defined PICO research question.	Adults with migraine, tension-type headache and cervicogenic headache (and mixed headache). Qualitative synthesis includes 26 studies and quantitative (meta-analysis) 20 studies. Six included RCTs were done with migraine patients: five investigated aerobic exercise or multidisciplinary treatment and one relaxation exercise: - Darabaneanu et al. 2011 - Dittrich et al. 2008 - Gunreben-Stempfleet al. 2009 - Lemstra et al. 2002 - Narin et al. 2003 - Varkey et al. 2009	Systematic review of randomized controlled studies and cross-over studies (data only from first phase before switch) on physiotherapy interventions. Review was done by following Cochrane handbook and PRISMA. Meta-analysis was conducted. Cochrane Risk of Bias was used. I2 statistics was used for heterogeneity. Cohen's kappa coefficient was used for evaluating inter- reviewer agreement, for study selection and risk of bias. Database search: PubMed/MEDLINE, EMBASE, PsychINFO, Cochrane Central Register of Controlled Trials, CINAHL, PEDro, hand search on relevant journals.	Aerobic exercise or combined intervention (physical and psychological) seems to be effective to decrease duration of migraine attack. Based on the review, physiotherapy interventions might be effective in reduction and prevention of headaches. Note: 17 of 26 studies had "high risk" of bias. Evidence certainty for all included studies was low (GRADE).

Effects on neuromodulation, acupuncture, and aerobic exercises on migraine and tension-type headache outcomes. A systematic review and meta-analysis.	Pi, C., Liu, Y., Li, L., Tang, W., Yan, X., & Yu, S. 2022. China. Medicine (IF 1.817).	"To quantify the effects of neuromodulation, acupuncture, and aerobic exercises in patients with migraine and tension-type headache". There was well defined PICO research question.	Adults with episodic migraine and tension-type headache. This review included 27 studies, of which three was aerobic exercise RCTs with migraine patients: - Hanssen et al. 2018 - Krøll et al. 2018 - Varkey et al. 2011	Systematic review of randomized controlled studies on neuromodulation, acupuncture, and aerobic exercises on migraine and tension-type headache outcomes. This review was done by following Cochrane handbook and PRISMA. Cochrane Risk of Bias was used. Meta-analysis was conducted. I2 statistics was used for heterogeneity. GRADE approach was used for making recommendations. Database search: PubMed, the Cochrane Central Register of Controlled Trials, Embase, and Chinese database China National Knowledge Infrastructure, WANFANG MEDICINE ONLINE, and Chinese Medical Journal database.	Aerobic exercise might decrease pain intensity within migraine patients and pain duration within tension-type headache patients. Neuromodulation might decrease pain intensity, duration, frequency and usage of acute medication within migraine patients. Acupuncture might decrease pain intensity and frequency in migraine patients, and usage of acute medication within tension-type headache patients. Note: Outcome measurements were heterogenic. Study quality (GRADE) was low to moderate.

AMSTAR 2 Quality Rating of the Included Systematic Reviews (Shea et al. 2017)

Study	Manual joint mobilization techniques, supervised physical activity, psychological treatment, acupuncture and patient education in migraine treatment. A systematic review and meta-analysis (Beier et al. 2022)	Efficacy of interventions used by physiotherapists for patients with headache and migraine—systematic review and meta-analysis (Luedtke et al. 2016)	Effects on neuromodulation, acupuncture, and aerobic exercises on migraine and tension-type headache outcomes. A systematic review and meta-analysis (Pi et al. 2022)
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes	Yes	Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes	Partial yes	Partial yes
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Yes	Yes
4. Did the review authors use a comprehensive literature search strategy?	Partial yes	Partial yes	Partial yes
5. Did the review authors perform study selection in duplicate?	Yes	Yes	Yes
6. Did the review authors perform data extraction in duplicate?	Yes	No	Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	No	No

8. Did the review authors describe the included studies in adequate detail?	Partial yes	Partial yes	Partial yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	Yes	Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	No	No	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes	Yes	Yes
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	Yes	Yes
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes	Yes	Yes
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Yes	Yes

15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes	Yes	Yes
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	Yes	Yes
Study quality	High	Low	Low

The Characteristics of Randomized Controlled Trials in Included Systematic Reviews

Study (included in systematic review)	**Number of participants**	**Intervention**	**Comparison**	**Follow up**	**Main results**
Darabaneanu, S., Overath, C. H., Rubin, D., Lüthje, S., Sye, W., Niederberger, U., Gerber, W. D., & Weisser, B. 2011. Aerobic exercise as a therapy option for migraine: a pilot study. *International Journal of Sports Medicine*, 32(6), 455–460. https://doi.org/10.1055/s-0030-1269928 (In systematic review by Luedtke et al. 2016)	16 patients with migraine with aura or migraine without aura.	Aerobic exercise 50 min three times a week for ten weeks.	No training.	Eight weeks.	Higher reduction in migraine days/month and lower intensity of attacks. Better improvement in fitness level led to better effectiveness on migraine.
Dittrich, S. M., Günther, V., Franz, G., Burtscher, M., Holzner, B., & Kopp, M. 2008. Aerobic exercise with relaxation: influence on pain and psychological well-being in female migraine patients. Clinical journal of sport medicine : *official journal of the Canadian Academy of Sport Medicine*, 18(4), 363–365. https://doi.org/10.1097/JSM.0b013e31817efac9 (In systematic reviews by Beier et al. 2022 and Luedtke et al. 2016)	30 patients with migraine with aura or migraine without aura.	Aerobic exercise 45 min and 15min muscle relaxation, three times a week for six weeks.	Information about exercise.	Six weeks.	Lower self-rated migraine pain intensity in intervention group. No change in frequency of migraine or thinking about pain.
Gunreben-Stempfle, B., Griessinger, N., Lang, E., Muehlhans, B., Sittl, R., & Ulrich, K. 2009. Effectiveness of an intensive multidisciplinary headache treatment program. *Headache*, 49(7), 990–1000. https://doi.org/10.1111/j.1526-4610.2009.01448.x (In systematic review by Luedtke et al. 2016)	80 patients with migraine and/or tension-type headache.	Multidisciplinary program 96 hours (Group 1) and 20 hours (Group 2) during eight weeks. Multidisciplinary program included individual and group therapy, including cognitive behavioral therapy, patient education, biofeedback therapy, aerobic exercise, strength and relaxation training.	Usual care.	22 weeks.	Reduction in migraine frequency and days in both groups, especially group 1.

Hanssen, H., Minghetti, A., Magon, S., Rossmeissl, A., Rasenack, M., Papadopoulou, A., Klenk, C., Faude, O., Zahner, L., Sprenger, T., & Donath, L. 2018. Effects of different endurance exercise modalities on migraine days and cerebrovascular health in episodic migraineurs: A randomized controlled trial. *Scandinavian Journal of Medicine & Science in Sports*, 28(3), 1103–1112. https://doi.org/10.1111/sms.13023 (In systematic reviews by Beier et al. 2022 and Pi et al. 2022)	48 patients with episodic migraine without aura.	High intensity training 4x4 min 90-95 % of Hrmax, twice a week for twelve weeks.	Moderate intensity training 70% of Hrmax for 45min.	After intervention.	High intensity training most effective for migraine day reduction and cerebrovascular health.
Krøll, L. S., Hammarlund, C. S., Linde, M., Gard, G., & Jensen, R. H. 2018. The effects of aerobic exercise for persons with migraine and co-existing tension-type headache and neck pain. A randomized, controlled, clinical trial. *Cephalalgia : an International Journal of Headache*, 38(12), 1805–1816. https://doi.org/10.1177/0333102417752119 (In systematic reviews by Beier et al. 2022 and Pi et al. 2022)	52 patients with minimum of “two attacks of migraine and a minimum of one day with TTH and a minimum of one day with NP per month”.	Aerobic exercise 45 mins three times a week for twelve weeks.	Control group.	Six months.	Reduction in both groups: migraine pain intensity, duration and frequency.
Lemstra, M., Stewart, B., & Olszynski, W. P. 2002. Effectiveness of multidisciplinary intervention in the treatment of migraine: a randomized clinical trial. *Headache*, 42(9), 845–854. https://doi.org/10.1046/j.1526-4610.2002.02202.x (In systematic review by Luedtke et al. 2016)	77 patients with chronic migraine pain for at least 6 months and migraine with or without aura .	Aerobic, strength and relaxation training, 18 group sessions during six weeks, dietary lecture, massage therapy	Waiting list.	Three months.	Self-perceived pain frequency, intensity and duration; also quality of life, health status, pain related disability and depression after three months in intervention group
Narin, S. O., Pinar, L., Erbas, D., Oztürk, V., & Idiman, F. 2003. The effects of exercise and exercise-related changes in blood nitric oxide level on migraine headache. *Clinical Rehabilitation*, 17(6), 624–630. https://doi.org/10.1191/0269215503cr657oa (In systematic review by Luedtke et al. 2016)	40 patients with migraine without aura.	Aerobic exercise 60 mins three times a week for eight weeks.	No intervention.	After intervention.	Improvement in both groups: Pain intensity, frequency, duration of pain. Quality of life improved in intervention group. Blood nitric oxide (NO) levels rose significantly in intervention group.

Oliveira, A. B., Ribeiro, R. T., Mello, M. T., Tufik, S., & Peres, M. F. P. 2019. Anandamide Is Related to Clinical and Cardiorespiratory Benefits of Aerobic Exercise Training in Migraine Patients: A Randomized Controlled Clinical Trial. *Cannabis and Cannabinoid Research*, 4(4), 275–284. https://doi.org/10.1089/can.2018.0057 (In systematic review by Beier et al. 2022)	50 patients with episodic migraine with or without aura.	Aerobic exercise 40 min three times a week for twelve weeks.	Waitlist.	After intervention.	Plasma anandamide reduced and cardiorespiratory fitness increased in both groups. Number of migraine days, migraine attacks, and acute medication use decreased significantly in intervention group. Significant decrease on anxiety, depression, anger, and fatigue in intervention group. Significant correlation with acute pain medication reduction, cardiorespiratory fitness and anandamide reduction.
Santiago, M. D., Carvalho, D.deS., Gabbai, A. A., Pinto, M. M., Moutran, A. R., & Villa, T. R. 2014. Amitriptyline and aerobic exercise or amitriptyline alone in the treatment of chronic migraine: a randomized comparative study. *Arquivos de neuro-psiquiatria*, 72(11), 851–855. https://doi.org/10.1590/0004-282x20140148 (In systematic review by Beier et al. 2022)	60 patients with chronic migraine.	Amitriptyline and aerobic exercise 40 min three times a week for twelve weeks.	Amitriptyline.	After intervention.	Headache frequency, moderate pain intensity, duration of attack, body mass index, Beck Depression and Anxiety Inventories significantly decreased in amitriptyline and exercise group.
Varkey, E., Cider, A., Carlsson, J., & Linde, M. 2009. A study to evaluate the feasibility of an aerobic exercise program in patients with migraine. *Headache*, 49(4), 563–570. https://doi.org/10.1111/j.1526-4610.2008.01231.x (In systematic review by Luedtke et al. 2016)	In the review, authors cite this article; however, in their Table 3. ("study characteristics), they refer to study details of Varkey et al. 2011; so most likely cause of citation error. (Luedtke et al. 2016, 480, 482, 492.) (Varkey et al. 2009 is one group study, not an RCT)				

Varkey, E., Cider, A., Carlsson, J., & Linde, M. 2011. Exercise as migraine prophylaxis: a randomized study using relaxation and topiramate as controls. *Cephalalgia : an International Journal of Headache*, 31(14), 1428–1438. https://doi.org/10.1177/0333102411419681 (In systematic reviews by Beier et al. 2022, Pi et al. 2022 and likely Luedtke et al. included this study despite their citation to Varkey 2009, see above)	91 patients with migraine with aura or migraine without aura.	Aerobic exercise 40 min three times a week (Group 1) and relaxation exercise 5-20 min (Group 2).	Daily topiramate.	Six months.	No significant difference within groups. Attack reduction was showed in all groups.

The Excluded Studies after Full Text Screening

Baillie, L. E., Gabriele, J. M., & Penzien, D. B. 2014. A systematic review of behavioral headache interventions with an aerobic exercise component. *Headache*, 54(1), 40–53.

Barber, M., & Pace, A. 2020. Exercise and Migraine Prevention: a Review of the Literature. Current Pain and Headache Reports, 24(8), 39.

Kubat-Knopp, H. 2016. Effektivitat von manueller therapie und aktiver therapie bei migrane, spannungskopfschmerz und zervikogenem kopfschmerz (Effectiveness of manual therapy and active therapy for migraine, tension headache, and cervicogenic headache). *pt Zeitschrift fuer Physiotherapeuten* 2016;68(3):30-39 2016;():

La Touche, R., Fernández Pérez, J. J., Proy Acosta, A., González Campodónico, L., Martínez García, S., Adraos Juárez, D., Serrano García, B., Angulo-Díaz-Parreño, S., Cuenca-Martínez, F., Suso-Martí, L., & Paris-Alemany, A. 2020. Is aerobic exercise helpful in patients with migraine? A systematic review and meta-analysis. *Scandinavian Journal of Medicine & Science in Sports*, 30(6), 965–982.

Lardon, A., Girard, M. P., Zaïm, C., Lemeunier, N., Descarreaux, M., & Marchand, A. A. 2017. Effectiveness of preventive and treatment interventions for primary headaches in the workplace: A systematic review of the literature. Cephalalgia : *an International Journal of Headache*, 37(1), 64–73.

Lemmens, J., De Pauw, J., Van Soom, T., Michiels, S., Versijpt, J., van Breda, E., Castien, R., & De Hertogh, W. 2019. The effect of aerobic exercise on the number of migraine days, duration and pain intensity in migraine: a systematic literature review and meta-analysis. *The Journal of Headache and Pain*, 20(1), 16.

Machado-Oliveira, L., da Silva Gauto, Y. O., de Santana Neto, F. J., da Silva, M. G., Germano-Soares, A. H., & Diniz, P. R. B. (2020). Effects of Different Exercise Intensities on Headache: A Systematic Review. *American Journal of Physical Medicine & Rehabilitation*, 99(5), 390–396.

Malik, Manoj. 2015. A systematic review on behavioral and physical treatment approaches in management of Migraine. *Romanian Journal of Physiotherapy*. 21. 19-29.

Mukhtar, N. B., Meeus, M., Gursen, C., Mohammed, J., De Pauw, R., & Cagnie, B. 2022. Effectiveness of Hands-Off Therapy in the Management of Primary Headache: A Systematic Review and Meta-Analysis. *Evaluation & the Health Professions*, 45(2), 183–203.

Song, T. J., & Chu, M. K. 2021. Exercise in Treatment of Migraine Including Chronic Migraine. *Current Pain and Headache Reports*, 25(3), 14.

Varangot-Reille, C., Suso-Martí, L., Romero-Palau, M., Suárez-Pastor, P., & Cuenca-Martínez, F. 2022. Effects of Different Therapeutic Exercise Modalities on Migraine or Tension-Type Headache: A Systematic Review and Meta-Analysis with a Replicability Analysis. *The Journal of Pain*, 23(7), 1099–1122.

Woldeamanuel, Y. W., & Oliveira, A. B. D. 2022. What is the efficacy of aerobic exercise versus strength training in the treatment of migraine? A systematic review and network meta-analysis of clinical trials. *The Journal of Headache and Pain*, 23(1), 134.