Is aerobic exercise helpful in patients with migraine? A systematic review and meta-analysis

Running head: Exercise therapy and migraine

Systematic review and meta-analysis

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ABSTRACT

Purpose: To assess the effects of aerobic exercise (AE) on patients with migraine in terms of pain intensity, frequency and duration of migraine, and quality of life.

Methods: A systematic review and meta-analysis of randomized controlled trials was conducted. Standardized mean differences (SMDs) and 95% confidence intervals (CIs) were calculated for relevant outcomes and were pooled in a meta-analysis using the random effects model.

Results: A total of 10 articles from 1950 to 2019 were included, involving 508 patients. The meta-analysis showed statistically significant differences in the decrease in pain intensity (5 studies, n=166; SMD=1.25; 95% CI 0.47–2.04), frequency (6 studies, n=214; SMD=0.76; 95% CI 0.32–1.2), and duration of migraine (4 studies, n=106; SMD=0.41; 95% CI 0.03–0.8), in the short term. In addition, the meta-analysis showed statistically significant differences in the increase in quality of life (4 studies, n=150; SMD=2.7; 95% CI 1.17–4.24), even though the Egger's test suggested significant evidence of publication bias for the analysis of quality of life (Intercept=5.81; t=6.97; p=.02).

Conclusions: There is low-moderate quality evidence that in patients with migraine AE can decrease the pain intensity, frequency, and duration of migraine and can also increase quality of life.

Keywords: Aerobic exercise, Migraine, Headache, Exercise therapy.
INTRODUCTION

Migraine is a disabling, recurrent, multifactorial, hereditary, neurovascular neurological disorder that can be defined as a type of disabling primary headache disorder. It is characterized by recurrent unilateral pulsatile headache, being considered one of the most disabling pathologies by Global Burden of Disease for the age group 15 to 49 years with an estimated global prevalence of 11.6%, being the first cause of disability under 50 years old and having much higher disability weight than tension-type headache. One third of migraine attacks are preceded by the aura. The aura can appear before or during the headache and is characterized by fully reversible focal neurological symptoms together with a cortical spread depression. The migraine headache itself is described by patients as a throbbing pain, with nausea and/or vomiting, photophobia, and/or phonophobia. There is implication of the trigeminovascular system and peripheral or central sensitization. The most frequent symptoms of this phase are fatigue, mood changes, muscle tenderness and altered perception to sensory stimuli.

Nonpharmacological approaches could be one of the safest options for these patients, considering the possible contraindications and adverse effects of migraine drugs. The pharmacological approach is the most recommended treatment in practice guidelines, but there is emerging evidence regarding the benefits of educational, psychological, manual therapy, and exercise interventions for patients with migraine, which also lack adverse effects. Previous studies had shown a correlation between low physical activity and increasing headache frequency but establishing which is the cause or the consequence is under discussion.

Aerobic exercise (AE) includes any activity of moderate intensity, such as walking quickly, running, or cycling in a continuous manner. The intensity can be estimated by the rate of energy expenditure during exercise (metabolic equivalents, METs) or by the percent of aerobic power used during the activity (hearth rate or percent of VO_{2max}). It has been suggested that AE may produce a phenomenon of exercise-induced hypoalgesia and has therefore been proposed as a treatment strategy in patients with pain due to its potential role in pain modulation both short and long term. In addition endogenous opioid could be lower in patients with chronic migraine but exercise can increase beta-endorphin levels and it is hypothesized that it activates the endogenous cannabinoid system through an emotional-motivational dimension. Finally, exercise has been shown to be effective in enhancing psychological and behavioral aspects, including self-efficacy, depressive symptoms, sleep regulation, mood, and outcome expectancies. One of the most relevant variables in migraine patients is quality of life. Several studies have shown that
migraine negatively affects the perception of quality of life. Variables such as the frequency or
duration of migraines, the perception of pain as well as associated symptoms such as nausea,
photophobia, phonophobia as well as mood disorders are able to affect quality of life on their own
regardless of the presence of more factors. Due to the importance of the impact of quality of life
on people's health, it is important to carry out an exhaustive evaluation both of the variable itself
and of all covariates that may independently affect it indirectly ²⁹–³⁴.

Therefore, the aim of the present review was to develop a systematic review and meta-analysis of
the effects of AE on patients with migraine regarding pain intensity, frequency and duration of
migraine, and quality of life. In addition, we aimed to identify the best exercise prescription to
help patients with migraine.

METHODS

This systematic review and meta-analysis was performed in accordance with the Preferred
Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines ³⁵. The
PRISMA statement is composed of a 27-item checklist and a 4-phase flow diagram, which assists
in reporting systematic reviews and meta-analyses ³⁵. PRISMA can be used to report systematic
reviews of various forms of research, most notably randomized controlled trials (Figure 1).

Inclusion criteria

The selection criteria used in this review were based on methodological and clinical factors, such
as the population, intervention, control, outcomes, and study design (PICOS) ³⁶ criteria as follows:

Population

The patients selected for the articles published were older than 18 years. All participants were
diagnosed with migraine with or without aura. The patients were diagnosed with migraine with or
without aura by the International Classification of Headache Disorders criteria. The patient's sex
was irrelevant.

Intervention and Control

The studies compared AE with other forms of exercise therapy and/or minimal usual care
(information, minimal education, maintenance of daily living activity, or drugs).

Outcomes

The measures used to assess the results and effects of exercise involved at least 2 or more of the
following headache-related outcome measures: Pain intensity, duration of headache attacks,
headache frequency or number of migraine days and measures of quality of life. The first three
were self-reported measures through diaries or questionnaires where patients recorded data about
the different variables and quality of life was reported through specific self-reported questionnaires. When the quality of life variable was evaluated in a multidimensional manner, the subscale related to physical aspects was selected. Assessments were performed before, during and after the aerobic exercise treatment. Furthermore, these had to be registered in the short term (<3 months) as proposed by the Cochrane Back Review Group. Short-term follow-up refers to outcomes that are measured closest to 4 weeks after randomization; it could be as short as 7 days in a trial of analgesics and as long as 12 weeks (3 months) in trials of exercise therapy such as those included in this review.37

Study design

Randomized controlled trials (RCTs) and quasi-randomized controlled trials (q-RCTs) were selected. No restrictions were applied to any specific language as recommended by the international criteria.38

Search strategy

The search for scientific articles was performed using PubMed (1950 to January 2019), EMBASE (1988 to January 2019), CINAHL (1982 to January 2019), and Google Scholar with an end date of January 20, 2019.

The PubMed search strategy used for database filters proposed by Haynes et al. were used to locate treatment studies, with a sensitivity of 99% and a specificity of 97%.39 EMBASE search strategy was made according to the combination of terms proposed by Wilczynski et al., 2005 with a sensitivity of 91.8% and specificity of 98.2%.40 In CINAHL, search terms were combined to optimize sensitivity and specificity (above 91% for both).41 Specific search strategy used for each database is shown in Appendix 1. In addition, the search was adapted and performed in Google Scholar due to its capacity to search for relevant articles and grey literature.42,43

Two independent reviewers conducted the search using the same methodology, and the differences that emerged in this phase were resolved by consensus. In addition, the reference sections of original studies were screened manually.

Selection criteria and data extraction

First, a data analysis was performed by 2 independent reviewers who assessed the relevance of the RCTs regarding the study questions and objectives. This first analysis was made based on information from the title, abstract, and keywords of each study. If there was no consensus or the abstracts did not contain sufficient information, the full text was reviewed.
In the second phase of the analysis using the full text, we proceeded to assess whether the studies met all of the inclusion criteria. Differences between reviewers were resolved by a process of discussion and consensus moderated by a third reviewer. Data described in the results were extracted by means of a structured protocol that ensured that the most relevant information was obtained from each study.

**Methodological quality assessment**

The risk of bias in the included studies was assessed by using the “Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0” (updated in 2011 by the Cochrane Organization). Risk of bias assessment of selected articles was performed using the Cochrane risk of bias tool for randomised controlled trials (RCTs). Items of the risk of bias assessment were classified as ‘+’, ‘-’ or ‘?’. An item was classified as “+” if it showed sufficient information and there was a low probability of bias. An item was classified as ‘-’ if, despite sufficient information being available, the article did not meet a specific criterion. Finally, an item was classified as “?” if the information was not clear enough. This assessment tool covers 7 domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other biases. Bias was assessed as “low risk,” “high risk,” or “unclear risk.”

Two independent reviewers examined the quality of all of the selected studies using the same methodology; disagreements between reviewers were resolved by consensus including a third reviewer. The inter-rater reliability was determined using a Kappa coefficient (>0.7 indicated a high level of agreement between assessors, between 0.5 and 0.7 a moderate level of agreement, and <0.5 a low level of agreement).

**Qualitative analysis**

The qualitative analysis was based on classifying the results into levels of evidence according to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE), which is based on 5 domains: study design, imprecision, indirectness, heterogeneity, and publication bias.

Evidence was categorized into the following 4 levels accordingly: (a) *High quality*. Further research is very unlikely to change our confidence in the estimate of effect. All 5 domains are also met; (b) *Moderate quality*. Further research is likely to have an important impact on our confidence in the estimate of effect and might change the estimate of effect. One of the 5 domains
is not met; (c) Low quality. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Two of the 5 domains are not met; and (d) Very low quality. Any estimate of effect is very uncertain. Three of the 5 domains are not met.\textsuperscript{46,47}

**Data synthesis and analysis**

The statistical analysis was conducted using meta-analysis with interactive explanations software (MIX, version 1.7)\textsuperscript{48}. To provide a comparison between outcomes reported by the studies, the standardized mean difference (SMD) over time and corresponding 95% confidence interval (CI) were calculated for the continuous variables. The statistical significance of the pooled SMD was examined as Hedges’ \( g \), to account for possible overestimation of the true population effect size in small studies\textsuperscript{49}.

The same inclusion criteria were used for the systematic review as well as for the meta-analysis, and 4 more criteria were included: (1) In the results, there was detailed information regarding the comparative statistical data of the exposure factors, therapeutic interventions, and treatment responses; (2) The exercise therapy intervention was compared with a control group; and (3) Data on the analyzed variables were represented in at least 2 studies.

The estimated SMDs were interpreted as described by Hopkins, Marshall, Batterham, & Hanin, 2009 that is, an SMD of 4.0 was considered to represent an extremely large clinical effect, 2.0 to 4.0 a very large effect, 1.2 to 2.0 a large effect, 0.6 to 1.2 a moderate effect, 0.2 to 0.6 a small effect, and 0.0 to 0.2 a trivial effect\textsuperscript{50}.

The degree of heterogeneity among the studies was estimated by the Cochran's \( Q \) statistic test (a \( P \) value <.05 was considered significant) and the inconsistency index (\( I^2 \))\textsuperscript{51}. \( I^2 >25\% \) was considered to represent small, \( I^2 >50\% \) medium, and \( I^2 >75\% \) large heterogeneity.\textsuperscript{52} The \( I^2 \) index is a complement to the \( Q \) test, although it has the same problems of power with a small number of studies.\textsuperscript{52}

When the \( Q \)-test was significant (\( P <.1 \)) and/or the result of \( I^2 \) is >75\%, this indicated that there was heterogeneity among the studies and the random-effects model was conducted in the meta-analysis.

To detect publication biases and test the influence of each individual study, a visual evaluation of the funnel plot and exclusion sensitivity plot, seeking asymmetry, was performed. Also, we employed Egger's regression tests to assess publication bias.\textsuperscript{53}
RESULTS

Methodological quality analysis

The quality of all the studies was evaluated with the Cochrane scale (Figures 2 and 3). Most importantly, 100% of the studies had a low risk of bias in the selective reporting. Other important findings were that 80% of the studies had a low risk of bias in the random sequence generation, and 70% of the studies had a low risk of bias in the incomplete outcome data. On the other hand, we found that 70% of the studies had a high risk of bias in the blinding of the participants and personnel. The inter-rater reliability of the methodological quality assessment was high (k=0.787).

Study population characteristics

The total number of participants was 508 (females: 462, males: 37). The patients were diagnosed with migraine with or without aura, and all the studies used the International Classification of Headache Disorders criteria with its different version except the Pairo’s et al., 2016 study. Descriptive characteristics of the studies included are presented in Table 1.

Interventions

Six of the studies had 2 groups: a moderate exercise and a control group. In the case of Hanssen et al.2018 there was a third group of intense exercisers. Medication was used in 2 studies: topiramate in Varkey et al., 2011 and amitriptyline in both groups of the study by Santiago et al.2014. Bond et al.,2018 employed 2 intervention groups: (1) exercise + diet and (2) migraine education. The exercise intervention in terms of the duration of each exercise session was 60 minutes or more for 2 studies and the rest used an intervention ranging from 40 to 50 minutes per session. The frequency of exercise was expected to be 3 times per week for most of the studies and only 2 times per week for 2 of them with the exception of Bond et al.,2018 who used a frequency of 5 times per week. Intervention characteristics of the studies included are presented in Table 2.

Adverse effects

Adverse effects were found in the studies that used medications. Four participants from the study of Santiago et al. 2014 had adverse effects due to amitriptyline intake (drowsiness and dry mouth), and in the study by Varkey et al.,2018 patients had adverse effects for topiramate (paresthesia, fatigue, depressed mood, vertigo, and infrequent bowel movements). No adverse effects were found for the patients in the exercise groups. Only 2 studies performed an intention to
treat analysis \(^{54,61}\) including \(^{62}\) even though they obtained a loss to follow-up greater than 20\%. In the rest of the studies, the losses to follow-up were less than 20\% \(^{55-60,63}\).

**Meta-analysis results**

**Frequency of migraine**

The frequency of migraine was measured by self-reports, which recorded the days per month that the patient suffered migraine \(^{54-63}\). All the studies measured the frequency in days/month except Kroll et al., 2018\(^{57}\) who measured frequency by weeks, and Disttrich et al., 2008\(^{55}\) who measured frequency by weeks and months. Three of these studies showed improvements in the exercise group \(^{55,57,59}\). In Hanssen et al., 2018\(^{56}\) these improvements were superior in the intense exercise group and in Santiago et al., 2014\(^{60}\) they were superior in the therapy combined with exercise group. In another 3 studies, improvements in both groups were found \(^{54,61,63}\). On the other hand, 2 studies did not obtain statistically significant results \(^{58,62}\).

The meta-analysis for the frequency of migraine showed statistically significant differences in the decrease in frequency in the short term. The estimated SMDs was considered to represent a moderate clinical effect in 6 studies \(^{56,57,59,61-63}\) \((n=214; \text{SMD}=0.76; 95\% \text{ CI} 0.32–1.2; \text{heterogeneity Q value}=13.18; P=.04; \text{inconsistency } I^2=54\%\)), and there was no evidence of publication bias in the meta-analysis \((SE=2.25; T=0.69; P=.52)\). In terms of frequency, the shape of the funnel plot appeared to be symmetrical in the dominant model as judged by visual examination (Figure 4). The influence of each individual study was assessed with a sensitivity exclusion analysis. Statistically strong results were obtained, given the analysis suggested that no individual study significantly affected the pooled SMD. The similarity found among the pooled estimates suggests that no single study influenced the results of the meta-analysis. Accordingly, Egger's test of asymmetry was applied and the results suggested no significant evidence of publication bias for the analysis of the frequency of migraine \((\text{intercept}=1.55; T=0.69; P=.52)\).

**Intensity of pain**

The visual analogue scale was used in all the studies \(^{54-63}\). In 6 studies, pain intensity showed improvements in the exercise group \(^{54,55,57,59,62,63}\). The improvement in the study by Lockett & Campbell., 1992 was not statistically significant.

At the same time, Santiago et al., 2014\(^{60}\) found better results in the therapy combined with exercise group, and Varkey et al., 2011\(^{61}\) found superior results in the first 3 months in the topiramate group.
The meta-analysis on pain intensity showed statistically significant differences in the reduction in intensity in the short term. The estimated SMDs was considered to represent a large clinical effect in 4 studies (n=166; SMD=1.25; 95% CI 0.47–2.04. heterogeneity Q value=18.19; $P=.001$; inconsistency $I^2=78\%$) and there was no evidence of publication bias in the meta-analysis (SE=−0.47; T=−1.23; $P=.3$). In terms of pain intensity, the shape of the funnel plot appeared to be asymmetrical in the dominant model as judged by visual examination (Figure 5). The influence of each individual study was assessed with a sensitivity exclusion analysis. Statistically strong results were obtained, given the analysis suggested that no individual study significantly affected the pooled SMD. The similarity found among the pooled estimates suggests that no single study influenced the results of the meta-analysis. Accordingly, Egger's test of asymmetry was applied and the results suggested no significant evidence for publication bias for the analysis of the intensity of pain (intercept=3.78; T=3.29; $P=.05$).

Duration of migraine

The duration of migraine was measured by self-reports in all the studies, which recorded the hours that the patient suffered migraine. Three studies showed improvements in the exercise group. Meanwhile, Santiago et al., 2014 found superior results in the combined therapy with exercise group. Another 2 studies found improvements in both groups. Lockett & Campbell, 1992 did not obtain statistically significant results.

The meta-analysis showed statistically significant differences in the decrease of the duration of migraine in the short term. The estimated SMDs was considered to represent a small clinical effect in 4 studies (n=106; SMD=0.41; 95% CI 0.03–0.8; heterogeneity Q value=2.38; $P=.5$; inconsistency $I^2=0\%$) and there was no evidence of publication bias for the meta-analysis (SE=1.15; T=2.06; $P=.17$). In terms of the duration, the shape of the funnel plot appeared to be symmetrical in the dominant model as judged by visual examination (Figure 6). The influence of each individual study was assessed with a sensitivity exclusion analysis (Figure 7). Statistically weak results were obtained, given the analysis suggested that 3 studies significantly affected the pooled SMD. However, the similarity found among the pooled estimates suggests that no single study influenced the results of the meta-analysis in a disproportionate manner. Egger's test of asymmetry was applied and the results suggested no significant evidence for publication bias for the analysis of the duration of migraine (intercept=2.36; T=2.06; $P=.17$).

Quality of life
Six articles found improvements in quality of life with each author using different measurement instruments (Table 1).

The meta-analysis for quality of life showed statistically significant differences in the increase in quality of life in the short term. The estimated SMDs was considered to represent a very large clinical effect in 4 studies (n=150; SMD=2.7; 95% CI 1.17–4.24; heterogeneity Q value=2.38; \( P = .5 \); inconsistency \( I^2 = 0\% \)); however, there was evidence of publication bias for the meta-analysis (SE=0.83; T=6.97; \( P = .02 \)). In terms of quality of life, the shape of the funnel plot appeared to be asymmetrical in the dominant model as judged by visual examination (Figure 8).

The similarity found among the pooled estimates suggests that no single study influenced the results of the meta-analysis. However, Egger's test of asymmetry was applied and the results suggested significant evidence of publication bias for the quality of life analysis (intercept=5.81; \( T = 6.97 \); \( P = .02 \)).

Qualitative analysis

According to the GRADE recommendations, there was low quality evidence regarding the effects of AE on migraine frequency and pain intensity, being downgraded due to quality and inconsistency. However, there was moderate quality evidence of the effects of AE on the duration of migraine attacks and on the impact of AE on quality of life being downgraded due to quality.

DISCUSSION

The aim of the present study was to systematically review the literature on the effects of AE on patients with migraine in variables such as frequency and duration of migraine, pain intensity, and quality of life, and then perform a meta-analysis when possible. A total of 10 studies were included in the systematic review, 6 of which were included in the posterior meta-analysis. The results obtained from the meta-analysis showed that exercise has a significant effect, obtaining statistically significant reductions in the frequency, intensity, and duration of pain, as well as a statistically significant improvement in quality of life. It is important to stress that there is a great deal of heterogeneity for studies analyzed, and there are significant concerns about bias.

Frequency of migraine

A reduction in the frequency of migraine attacks has been observed after AE training. Almost all the studies included in this systematic review found AE to be an intervention capable of reducing migraine frequency. Despite the reported reduction, nonsignificant differences were found between the intervention and control groups in some studies. Hanssen et al., 2018, Darabaneanu et al., 2011, Krøll et al., 2018 and Narin et al., 2003 have shown a significant
reduction of more than 1 day per month in migraine frequency in the exercise group. These results are also clinically relevant, given a previous study stated that a 1 day per month reduction in headache frequency is the minimal difference needed to be clinically meaningful.

The data obtained in the present study are in accordance with those reported by Lemmens et al., 2019 who had observed a reduction in migraine days per month in favor of the intervention group. However, these authors did not analyze other variables of great relevance such as quality of life. In addition, Luedtke et al., 2016 had found a decrease in migraine frequency, however when they included additional studies with high risk of bias to their meta-analysis, changes in the results did not appear to be statistically significant. Supporting these findings, Overath et al., 2014 had observed a reduction in migraine days in patients who completed a 10-week AE program.

### Pain intensity

Regarding pain intensity, reductions in pain levels related to AE performance were found, and 8 of 9 studies included in the systematic review support AE as an effective intervention for decreasing pain intensity in patients with migraine. Lemmens et al., 2019 have shown a pain reduction of 20% to 54% in 3 studies included in their systematic review, but they did not perform a meta-analysis for this outcome. In addition, Amin et al., 2018 have reported improvements in pain intensity related to migraine and physical activity. On the other hand, Koltyn et al., 2014 had found nonsignificant changes in pain intensity when they performed their meta-analysis, which included trials with a high risk of bias.

### Duration of migraine

Duration of pain was measured by self-report in hours per month. Both in the systematic review and meta-analysis, an overall significant reduction was observed for this outcome after the AE intervention. Luedtke et al., 2016 had found a statistically significant reduction in pain duration. Pain duration is not described as a primary outcome in many studies; thus, it is difficult to compare this variable with our results. However, AE has been studied in other chronic conditions as an effective approach for pain management.

### Quality of life

Increased quality of life was found in 5 of the 6 studies included in the systematic review after AE intervention compared with the control group. Bond et al., 2018 did not find changes in this outcome; however, only recommendations for exercise, and not a structured exercise intervention for the intervention group were provided, which could be one of the reasons for this result.
The manner of assessing quality of life was different in each study included in the systematic review; thus, heterogeneity is a factor to consider in this outcome. In contrast to Lemmens et al., 2019, our systematic review and meta-analysis aimed to analyze the quality of life changes produced by AE, given a reduction in quality of life is commonly present in patients with migraine 69,70. To our knowledge, this is the first SR and MA to analyze this variable. Quality of life is related to subjective health perception including individual physical and mental health relationships and their functional status. It is therefore that quality of life includes the individual's satisfaction with his or her state of health and the emotional response given to it 34. The results obtained are in line with previous literature, which suggests that an increase in this variable would represent an improvement in other qualitative variables 71. These results suggest that AE led to improvements in variables such as pain intensity, pain frequency and duration of migraine, and also resulted in a significant increase in quality of life and therefore, in the subjective perception of health in migraine patients.

The role of exercise
The role of AE in migraine management is supported by multiple lines of evidence. Nevertheless, the mechanisms by which exercise can be effective in treating migraines remain unclear 72. It has been speculated that the mechanisms involved in aerobic training could be related to changes in inflammatory and neurovascular pathways, as well as to psychological, behavioral, and sociocognitive factors 27,67.

AE training might increase endorphin levels and neurotransmitter, so the improvements could be mediated by an increase in endorphin levels and improvements in the function of neurotransmitters 27,66. Some of the latter play a role in the pathogenesis of migraine, since a dysfunction in the antinociceptive system can be hypothesized in these patients. Increases in endogenous opioids and endocannabinoids involve the activation of descending inhibitory pathways following AE, what produces analgesia. Opioid and endocannabinoid systems are activated when exercise is performed in healthy subjects 21, however, endocannabinoid system has been observed to be intensity-dependent, what means that moderate-intensity exercise leads to greater increases in circulating anandamide levels compared with a moderate speed walk and high-intensity run 67,73.

Other mechanisms related to AE are the modulating effects it exerts over affective, cognitive, and motivational aspects of pain 67,72. Improvements in psychological sphere (changes in self-efficacy and self-esteem following AE) may be involved 27. The anti-depressant effects of the aerobic
exercise may share similar biological and psychological mechanisms for which improvements in migraine may occur. Thus, this could explain in part, the anti-depressant effects of aerobic exercise\(^\text{27}\).

In this regard, AE can also be considered a stressor for migraine patients, both physiologically and psychologically. The manner in which the participant perceives the exercise can significantly influence the results obtained\(^\text{74,75}\). As mentioned by Koseoglu et al.,\text{2015} it is improbable that a single factor would be the responsible of exercise-induced changes in migraine. Instead, all of the mentioned factors (biological, psychological and behavioral), may possibly be involved and correlated with each other\(^\text{15}\). Finally, no adverse effects were reported for AE in any of the studies included in the present review. In addition, engagement in an AE program might lead to positive overall health benefits following exercise\(^\text{68}\).

Limitations

This study has some limitations. Although a systematic search strategy was followed, the risk of selection bias might still be present. Another limitation is the quality of the included studies, due to their methodological designs (i.e., different interventions in control groups or the lack of a control group). Also, 3 quasi-experimental controlled clinical trials were included in the systematic review and 2 of them in the meta-analysis\(^\text{62,63}\). The best results were obtained in those studies in which there was no randomization of the participants, thus no regular distribution at baseline, implying a high risk of bias. Another is the possible risk of selection bias present in the included studies; thus, the sample might not be representative of the population intended for analysis.

CONCLUSIONS

This meta-analysis suggests that there is low-quality evidence that in patients with migraine, AE can decrease the pain intensity and frequency. Additionally, there is moderate quality evidence that AE can decrease the duration of migraine and improve quality of life. Findings of this study should be considered with caution due to the great heterogeneity and bias found, so standardized outcome measures are recommended in future studies to obtain stronger conclusions.

Perspective

Aerobic exercise has a significant effect in the frequency, intensity, and duration of pain, as well as a improvement in quality of life in patients with migraine, although the evidence found is low/moderate quality. No adverse effects were reported in any of the studies, so aerobic exercise in patients with migraine should be clinically considered.
Future studies

Below, we propose a series of suggestions that we believe should guide future studies that address migraine problems through exercise. First, more comparisons between the two types of moderate exercise and high-intensity exercise would be needed.

In addition to this, a cluster should be made to be able to classify the patients who improve and those who do not improve through the application of exercise. This would involve more studies to investigate why a group of patients with migraine does not improve through exercise.

Finally, it would be interesting for those patients with psychosocial factors associated with migraine to use other exercise models based on a biobehavioral model such as graduated exposure or graduated exercise.

Conflicts of Interest

The authors declare that they have no conflicts of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
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**FIGURE CAPTIONS**

**Figure 1.** Flow chart of participant selection according to PRISMA.

**Figure 2.** Risk of bias summary: Review authors’ judgements about each risk of bias item for each included study (Risk of Bias scale).

**Figure 3.** Risk of bias graph: Review authors’ judgements about each risk of bias item presented as percentages across all included studies (Risk of Bias scale).

**Figure 4.** Publication bias heterogeneity funnel plot for frequency of migraine. A funnel plot was used to assess the risk of publication bias. The diagonal lines represent the 95% confidence limits. SMD: standardized mean difference. Synthesis forest plot for frequency of migraine. This forest plot summarizes the results of 6 included studies (sample size, standardized mean differences [SMDs], and weight). The small boxes with the squares represent the point estimate of the effect size and sample size. The lines on either side of the box represent a 95% confidence interval (CI).

**Figure 5.** Publication bias heterogeneity funnel plot for intensity of pain. A funnel plot was used to assess the risk of publication bias. The diagonal lines represent the 95% confidence limits. SMD: standardized mean difference. Synthesis forest plot for pain intensity. This forest plot summarizes the results of 5 included studies (sample size, standardized mean differences [SMDs], and weight). The small boxes with the squares represent the point estimate of the effect size and sample size. The lines on either side of the box represent a 95% confidence interval (CI).

**Figure 6.** Publication bias heterogeneity funnel plot for duration of migraine. A funnel plot was used to assess the risk of publication bias. The diagonal lines represent the 95% confidence limits. SMD: standardized mean difference. Synthesis forest plot for duration of migraine. This forest plot summarizes the results of 4 included studies (sample size, standardized mean differences [SMDs], and weight). The small boxes with the squares represent the point estimate of the effect size and sample size. The lines on either side of the box represent a 95% confidence interval (CI).

**Figure 7.** Exclusion sensitivity plot for duration of migraine. A random-effects model was used.

**Figure 8.** Publication bias heterogeneity funnel plot for quality of life. A funnel plot was used to assess the risk of publication bias. The diagonal lines represent the 95% confidence limits. SMD: standardized mean difference. Synthesis forest plot for quality of life. This forest plot summarizes the results of 4 included studies (sample size, standardized mean differences [SMDs], and weight). The small boxes with the squares represent the point estimate of the effect size and sample size. The lines on either side of the box represent a 95% confidence interval (CI).
APPENDIX

Appendix 1. Specific search strategy

PubMed

EMBASE
'migraine disorders'/exp OR 'migraine without aura'/exp OR 'migraine with aura'/exp AND 'exercise'/exp OR 'exercise therapy'/exp OR 'aerobic therapy'/exp OR 'high-intensity interval training'/exp OR 'exercise rehabilitation'/de OR 'physical activity'/de OR 'physical exercise'/de AND 'quality of life'/exp OR 'pain measurement'/exp OR 'visual analogue pain scale'/exp OR 'headache frequency'/de OR 'pain intensity'/de

Cinahl
TI ( "migraine disorders" OR "migraine without aura" OR "migraine with aura" AND "exercise" OR "exercise therapy" OR "aerobic exercise" OR "high-intensity interval training" OR "exercise rehabilitation" OR "physical activity" OR "physical exercise" AND "quality of life" OR "pain measurement" OR "visual analogue scale" OR "headache frequency" OR "pain intensity") OR AB ("migraine disorders" OR "migraine without aura" OR "migraine with aura" OR "exercise" OR "exercise therapy" OR "aerobic exercise" OR "high-intensity interval training" OR "exercise rehabilitation" OR "physical activity" OR "physical exercise" AND "quality of life" OR "pain measurement" OR "visual analogue scale" OR "headache frequency" OR "pain intensity")
Table 1. Characteristics of the included studies.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Gender</th>
<th>Participant ages, BMI (Kg·m(^{-2})) and duration of complaint</th>
<th>Study design and Intervention</th>
<th>Control</th>
<th>Outcome measures</th>
<th>Follow-up</th>
<th>Results and conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dittrich SA, et al. 2008(^{55})</td>
<td>30 females</td>
<td>Age EG (mean): 33.7±12.5, Age CG (mean): 32.1±12.1</td>
<td>RCT: EG (n=15)</td>
<td>RCT: CG (n=15):</td>
<td>- Body image scale (FKB-20)</td>
<td>- Sensational and affective dimensions of pain (SES)</td>
<td>Depression (BDI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Migraine with and without aura according to ICHD-II.</td>
<td></td>
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</tr>
<tr>
<td>Hanssen H, et al. 2017(^{56})</td>
<td>45 females</td>
<td>Age (mean): 36±10</td>
<td>RCT: HIIT (n=15)</td>
<td>RCT: CG (n=15):</td>
<td>- Migraine frequency</td>
<td>- Retinal vessel diameters (AVR)</td>
<td>- HIIT: 2</td>
</tr>
</tbody>
</table>
(BMI) = 22.3 ± 3.0
- MCT

(BMI) = 23.6 ± 8.7
- Episodic migraine without aura according to ICHD-IIIb

Maintaining their habitual physical activity

Maximal exercise testing (VO\(_2\)\(_{\text{max}}\))

- CG: 3

Non-intervention related injuries, pregnancy, non-compliance

Increase in AVR due to arteriolar dilatation in the HIIT group and due to venular constriction in the MCT.

Likely beneficial effects in VO\(_2\)\(_{\text{max}}\) in the HIIT group compared with the others.

**Kroll LS, et al. 2018**

<table>
<thead>
<tr>
<th></th>
<th>EG: 23 women; 3 men. Mean age 42 ± 10.9</th>
<th>RCT: 36 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>CG</td>
<td>23 women; 3 men. Mean age 36 ± 10.1</td>
<td>- Headache diary (number of days with headache, type of headache, pain intensity, duration, and intake of acute medication) - Physical activity level (IPAQ) - Quality of life</td>
</tr>
<tr>
<td>Minimum of two attacks of migraine and a</td>
<td></td>
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</tr>
</tbody>
</table>

Losses: EG (n=0) CTG (n=0)

AE reduced migraine days from 9.2 at baseline to 7.2 after 3 months (\(P=.025\)), also observed at follow-up (\(P<.05\)). No between-group differences.
minimum of one day with TTH and a minimum of one day with NP per month. (WHO-5)
- Impact of migraine, tension type headache, and neck pain
- Physical fitness (VO$_{2\text{max}}$)

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Ages (mean)</th>
<th>RCT:</th>
<th>Baseline 4 weeks before intervention.</th>
<th>4 weeks after intervention</th>
<th>Improvements:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pairo, Parnow, Sari-aslani, &amp; Eslami, 2016</td>
<td>20 females</td>
<td>-EG: 38.3 ± 5.7, -CG: 32.4 ± 5.7</td>
<td>-EG (n=10)</td>
<td>Migraine status (Headache questionnaire: frequency, duration, and intensity)</td>
<td>Migraine status</td>
<td>Significant improvements in all outcome measures ($P&lt;.001$) except in WHR.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-CG (n=10):</td>
<td>Quality of life (HIT-6)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>without intervention</td>
<td>Body composition factors (Body composition, BMI, WHR)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Maximal oxygen uptake (VO$_{2\text{max}}$)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Losses:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Data</td>
<td>Age (mean):</td>
<td>Study Design</td>
<td>Baseline</td>
<td>Post-treatment (end of the 3rd month)</td>
<td>Losses</td>
</tr>
<tr>
<td>-------------------------------------------</td>
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</tr>
<tr>
<td>Santiago et al., 2014&lt;sup&gt;60&lt;/sup&gt;</td>
<td>60</td>
<td>Ages (mean):</td>
<td>RCT: EG1 (n=30): amitriptyline</td>
<td>Baseline</td>
<td>Post-treatment (end of the 3rd month)</td>
<td>Losses:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>35±8 (26 females)</td>
<td>EG2 (n=30): amitriptyline and AE</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>31±9 (24 females)</td>
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<tr>
<td></td>
<td></td>
<td>Chronic migraine</td>
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<td></td>
<td></td>
<td>ICHD-II</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>-EG1 (BMI)=24.0±2.6</td>
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<td>6</td>
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<tr>
<td></td>
<td></td>
<td>-EG2 (BMI)=24.0±2.5</td>
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<td></td>
<td>7</td>
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</tr>
<tr>
<td>Varkey, Cider, Carlsson, &amp; Linde, 2011&lt;sup&gt;61&lt;/sup&gt;</td>
<td>91</td>
<td>Ages (mean):</td>
<td>RCT: EG1 (n=30)</td>
<td>Headache diary</td>
<td>-last month</td>
<td>All group reduced the frequency of migraine attacks. Only in the topiramate group were</td>
</tr>
<tr>
<td></td>
<td></td>
<td>41.5±11.4 (82 females)</td>
<td></td>
<td>4 weeks before</td>
<td>of treatment</td>
<td>cervical pain reduction.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-EG1: 47.0±10.8</td>
<td></td>
<td>Baseline and</td>
<td>treatment</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>-EG2: 44.4±9.2</td>
<td></td>
<td>treatment period:</td>
<td>-3 months</td>
<td></td>
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</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Group</th>
<th>Intervention</th>
<th>Duration</th>
<th>Measures</th>
<th>Losses</th>
</tr>
</thead>
<tbody>
<tr>
<td>EG1</td>
<td>Maximum of 200 mg/day</td>
<td>12 weeks</td>
<td>Migraine Status (headache diary), Quality of Life (MSQoL), Maximal Oxygen Uptake (VO\textsubscript{2max}), Physical activity level (IPAQ)</td>
<td>CG (n=4), EG1 (n=5), EG2 (n=10)</td>
</tr>
<tr>
<td>EG2</td>
<td>6 exercises, each exercise 5–20 min daily</td>
<td>12 weeks</td>
<td>Migraine Status (headache diary), Quality of Life (MSQoL), Maximal Oxygen Uptake (VO\textsubscript{2max}), Physical activity level (IPAQ)</td>
<td>CG (n=7), EG1 (n=8), EG2 (n=11)</td>
</tr>
<tr>
<td>CG</td>
<td>Maximum of 200 mg/day</td>
<td>12 weeks</td>
<td>Migraine Status (headache diary), Quality of Life (MSQoL), Maximal Oxygen Uptake (VO\textsubscript{2max}), Physical activity level (IPAQ)</td>
<td>CG (n=16), EG1 (n=14), EG2 (n=11)</td>
</tr>
</tbody>
</table>

Frequency of 2–8 attacks per month, and duration ≥1 year. ICHD-II

No adverse effects found.
Bond et al., 2018

**Participants:**
- Population: 110 women
- EG1: 54 women, Mean age: 38.5 ± 7.4 years
- EG2: 56 women, Mean age: 40.0 ± 8.4 years
- Total (BMI) = 35.6 ± 7.7

**Intervention:**
- RCT
- EG1: Migraine education, 16–20 weeks
- EG2: Migraine education, 16–20 weeks

**Outcome Measures:**
- Baseline (recording of the 4 weeks before intervention)
- Post-treatment (16–20 weeks after baseline)
- Headache diary (frequency, pain intensity and duration)
- Quality of life (HIT-6)
- Body composition factors

**Follow-up:**
- Losses: EG1: 8, EG2: 11
- Losses: EG1: 11, EG2: 14

An improvement in headache frequency was found in both groups. No difference between groups.

Darabaneanu, 2011

**Participants:**
- Population: 16
- EG: 15 women, 2 men
- Mean age: 26 years

**Intervention:**
- QE
- CG

**Outcome Measures:**
- Baseline
- Post intervention (10 weeks)

The AE program improved the number of migraine headache days in the last 3 months. ICHD-III.
<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Age Range</th>
<th>Group</th>
<th>Measurements</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lockett DC, 1992&lt;sup&gt;58&lt;/sup&gt;</td>
<td>20 females</td>
<td>19–50</td>
<td>QE (n=11)</td>
<td>- Headache diary (frequency, duration, intensity) EG (n=0)</td>
<td>Those participants who improved their cardiovascular fitness perceived their migraines as less</td>
</tr>
<tr>
<td></td>
<td>EG (mean): 32.5</td>
<td></td>
<td>- CG (n=9)</td>
<td>- Impact of migraines (MPI) CG (n=0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CT (mean): 32.2</td>
<td></td>
<td>After the study</td>
<td></td>
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<tr>
<td></td>
<td>Women with QE</td>
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<tr>
<td></td>
<td>QE</td>
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<tr>
<td></td>
<td>CG</td>
<td></td>
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</tr>
</tbody>
</table>

This program also benefits patients with good motivation and physical fitness more. In addition, the increase in fitness level can be a predictor for the improvement of migraine.
<table>
<thead>
<tr>
<th>Narin, Pinar, Erbas, Oztürk, &amp; Idiman, 2003[^63]</th>
<th>40 females</th>
<th>Ages (mean): - EG: 35.20 ± 10.23 - CG: 40.0 ± 8.3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Common migraine without aura, at least 4 attacks per month</td>
<td>Classical migraines. ICHD</td>
</tr>
<tr>
<td></td>
<td>finished, aerobics classes were given</td>
<td>- Physical activity level (PAR-Q) - Physical activity level (CAFT)</td>
</tr>
<tr>
<td></td>
<td>QE - EG (n=20 women) - CG (n=20 women): medical treatment daily</td>
<td>Baseline Postintervention - Pain intensity (VAS) - Disability (PDI) - Quality of life scale (Grading the severity of chronic pain) - Nitric oxide analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Losses: - EG (n=0) - CG (n=0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Significant improvements were found in both groups for all variables (P&lt;.05). Pain intensity showed a greater reduction in the exercise group.</td>
</tr>
</tbody>
</table>

AE: aerobic exercise; RCT: randomized controlled trial; EG: exercise group; CG: control group; HIIT: high intensity interval training; MCT: moderate continuous aerobic training; QE: quasi-experimental study; ICHD: The International Classification of Headache Disorders criteria; VAS: visual analogue scale; PDI: Pain Disability Index; MSQoL: Migraine Specific Quality of Life questionnaire; HIT-6: Headache Impact Test; BMI: body mass index; WHR: waist-hip ratio; IPAQ: International Short Physical Activity Questionnaire; BDI: Beck Depression Inventory; SES: Schmerzempfindungs-Skala; FKB-20: Fragebogen zum Korperbild; PLC: Profil der Lebensqualitat chronisch Kranker; CRAE: central retinal arteriolar; CRVE: central retinal venular; AVR:
arterial to venular ratio; WHO-5: Well-Being Index; PPT: pressure pain threshold; B-L: Beschwerdeliste; SVF: Stress-Verarbeitungs – Fragebogen; FPI: Freiburger-Persönlichkeits-Inventar; PAR-Q: Physical Activity Readiness Questionnaire; CAFT: Canadian Aerobic Fitness Test; MPI: multidimensional pain inventory; BWL: behavioral weight loss.
<table>
<thead>
<tr>
<th>Trial</th>
<th>Group</th>
<th>Distribution</th>
<th>Frequency</th>
<th>Duration</th>
<th>Intensity</th>
<th>Exercise testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dittrich SA, et al.</td>
<td>Exercise</td>
<td>- Warm up = 5 min</td>
<td>Twice a week during 6 weeks</td>
<td>Total duration = 60 min of exercise</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2008</td>
<td>Group</td>
<td>- Aerobic exercise including training of coordination = 15–25 min</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>- Strength training = 10–20 min</td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td>- Stretching = 5 min</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>- Progressive muscle relaxation = 15 min</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Hanssen H, et al.</td>
<td>HIT</td>
<td>4-minute intervals repeated four times.</td>
<td>Twice a week over a 12 weeks</td>
<td>Intervals of 4 minutes followed by an active rest period of 3 minutes at 70% of HRmax</td>
<td>Intensity of 90 to 95% HRmax (± 5 bpm)</td>
<td>- Individual anaerobic lactate-threshold</td>
</tr>
<tr>
<td>2017</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Maximal HR</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>- VO2max (supervised)</td>
</tr>
<tr>
<td></td>
<td>MCT</td>
<td></td>
<td></td>
<td>45 minutes</td>
<td>HR of 70% (± 5 beats per minutes, bpm) of HRmax</td>
<td></td>
</tr>
<tr>
<td>Author(s)</td>
<td>Exercise Group</td>
<td>Description</td>
<td>Control Group</td>
<td>Exercise Intensity Based on</td>
<td>Duration</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Kroll LS, et al. 2018&lt;sup&gt;57&lt;/sup&gt;</td>
<td>Exercise Group</td>
<td>10 min warmup, 30 min endurance training, 5 min cool down</td>
<td>Control Group</td>
<td>Borg’s scale of Perceived Exertion. Warm up: 11-13, Endurance training: 14-16, Cool down: 11-13</td>
<td>Total duration=45 min of exercise</td>
<td></td>
</tr>
<tr>
<td>Pairo, Parnow, Sarialaslani, &amp; Eslami, 2016&lt;sup&gt;59&lt;/sup&gt;</td>
<td>Exercise Group</td>
<td>Moderate exercise of aerobic exercise: 10 min warm up, 20 basic exercise, 10 min cool down</td>
<td>-</td>
<td>(45%–60% VO&lt;sub&gt;2max&lt;/sub&gt;) (supervised)</td>
<td>Total duration=40 min of exercise</td>
<td></td>
</tr>
<tr>
<td>Santiago et al., 2014&lt;sup&gt;60&lt;/sup&gt;</td>
<td>Exercise Group</td>
<td>Fast walk</td>
<td>-</td>
<td>-</td>
<td>Total duration=40 min of exercise</td>
<td></td>
</tr>
<tr>
<td>Varkey, Cider,</td>
<td>Exercise Group</td>
<td>Exercise (15-min)</td>
<td>-</td>
<td>-</td>
<td>Total Exercise</td>
<td></td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Study</th>
<th>Group</th>
<th>Exercise Protocol</th>
<th>Exercise Frequency</th>
<th>Duration</th>
<th>Heart Rate</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carlsson, &amp; Linde, 2011&lt;sup&gt;61&lt;/sup&gt;</td>
<td>Warm-up: 11-13</td>
<td>Warm-up: 11-13</td>
<td>Exercise: 14-16</td>
<td>Cool-down: 11-13</td>
<td>40 min of exercise</td>
<td>Intensity based on Borg’s scale of Rated Perceived Exertion (6-20)</td>
</tr>
<tr>
<td>Bond et al., 2018&lt;sup&gt;64&lt;/sup&gt;</td>
<td>Control Group</td>
<td>Relaxation (6 exercises, each exercise 5–20 min)</td>
<td>Daily</td>
<td>30-120 min</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Exercise Group</td>
<td>Moderate exercise</td>
<td>5 days/week.</td>
<td>Total duration=50 min of exercise</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Darabaneanu S, 2011&lt;sup&gt;62&lt;/sup&gt;</td>
<td>Control Group</td>
<td>Maintain daily living activity</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Exercise Group</td>
<td>10 min warmup, 30 min jogging within an aerobic heart rate range and 10 min cool-down</td>
<td>3 times/week for 10 weeks</td>
<td>Total duration=50 min of exercise</td>
<td>150 bpm</td>
<td>HR</td>
</tr>
<tr>
<td>Lockett DC, 1992&lt;sup&gt;58&lt;/sup&gt;</td>
<td>Exercise Group</td>
<td>10 min warmup, 25 min</td>
<td>3 times/week for 6 weeks</td>
<td>Total</td>
<td>Active exercise</td>
<td>-</td>
</tr>
</tbody>
</table>
**Control Group**

<table>
<thead>
<tr>
<th>Activity</th>
<th>Duration</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintain daily living activity</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**Exercise Group**

Narin, Pinar, Erbas, Oztürk, & Idiman, 2003<sup>63</sup>

<table>
<thead>
<tr>
<th>Activity</th>
<th>Duration</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 min warmup, 10 min cycling, 10 min walking on treadmill, 5 min stepper, 10 min training upper extremities at the power station, 10 repetitions of neck and postural exercises, 10 repetitions of rowing and 5 min of cool-down</td>
<td>3 sessions/week for 8 weeks</td>
<td>Total duration=60 min of exercise</td>
</tr>
</tbody>
</table>

**Notes:**
- HIIT: High intensity interval training group
- MCT: Moderate continuous training
- BMI: Body mass index
- HR: Heart rate
- bpm: beats per minute
Figure 1. Flow chart of participant selection according to PRISMA
<table>
<thead>
<tr>
<th>Study</th>
<th>Random Sequence Generation</th>
<th>Allocation Concealment</th>
<th>Blinding of Participants and Personnel</th>
<th>Blinding of Outcome Assessment</th>
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