Headache Medicine

Review

Does running reduce the frequency and intensity of migraine attacks? A systematic review with meta-analysis

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Edited by:
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Abstract

Introduction
Migraine is a complex headache to treat, often with an unsatisfactory clinical response. Aerobic exercise, such as running, can be a non-pharmacological treatment to reduce migraine attacks.

Objective
This systematic review with meta-analysis investigated the effects of running on frequency and intensity of pain in subjects with migraine compared with other or no aerobic exercise.

Methods
Randomized and quasi-randomized clinical trials were searched between September and November 2021 in BVS, PubMed, Cochrane, CINAHL, SCOPUS, Embase, and Web of Science databases. The Cochrane Risk of Bias tool assessed methodological quality, and the recommendation ranking assessed the certainty of evidence. The frequency of migraine attacks was pooled in a meta-analysis (random effects) that included interval and continuous running subgroups.

Results
Only two of the 483 studies analyzed were included in the review (52 individuals, 81% females). Migraine intensity was not included in the meta-analysis because only one study measured this outcome. None of the studies demonstrated that running reduced the frequency of migraine attacks (MD = -0.40 [95% CI = -1.61 to 0.81]). The studies included presented a high risk of bias and very low certainty of evidence.

Conclusion
The results were not sufficient to recommend running as a treatment to reduce the frequency and intensity of migraine attacks.

Introduction

Migraine is a primary and highly prevalent neurological disorder ranked in the top fourteen headaches by the International Headache Society (IHS).[1,2] According to the Institute for Health Metrics and Evaluation, migraine is the sixth cause of years lived with disability in individuals of any age and the first cause under the age of 50,[3] affecting about 15% of adults.[4,5] This disease is the second most common among adults in Brazil and is more disabling than depression, osteoarthritis, and diabetes.[6] It also impacts the individual and society economy through direct (e.g., medical care and medicines) and indirect costs (decreased productivity and absenteeism).[7]

Migraine treatment comprises the control of acute symptoms, use of prophylactic and therapeutic drugs, control of comorbidities, and reduction of exposure to triggering factors. Non-pharmacological treatments (*e.g.*, physical therapy, acupuncture, and meditation)[8-10] and aerobic exercises are used to mitigate migraine attacks in individuals who do not respond satisfactorily to drug treatment.[11-13]

Several authors mentioned that aerobic exercise increased the peripheral levels of β endorphins, serotonergic receptors, and sympathetic activity, leading to pain inhibition.[14-16] Therefore, these changes in pathophysiological pathways[17] might reduce pain in individuals with migraine who do not respond satisfactorily to the drug treatment.

According to the American College of Sports Medicine (ACSM), aerobic exercise is a rhythmic and continuous exercise that uses oxygen from the cardiorespiratory system to produce energy for the skeletal muscles.[18-20] Running, walking, dancing, and cycling[21-25] are the main modalities chosen by those who practice physical exercise. However, the training is considered aerobic when performed at an intensity established by the ACSM.[26]

The literature is unclear on which aerobic exercise would be most effective in reducing the frequency and intensity of migraines.[27,28] Among the main aerobic exercises, running has been evidenced since the 1970s,[29] and in the last twenty years,[30] more individuals have been running or participating in sporting events worldwide.[31] Therefore, considering the search for new strategies for the treatment of individuals with migraine, running is an easy-to-implement and low-cost sport.

This systematic review investigated the effects of running on the frequency and intensity of migraine with or without aura compared with other or no aerobic exercise in adults. The study question was, "Is running effective in reducing the number of days and intensity of migraine compared with walking, dancing, cycling, or no aerobic exercise?"

Methods

The study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).[32] The systematic review protocol was registered in the International Prospective Register of Systematic Reviews (Identifier: CRD42021269260).

Eligibility criteria

The Population, Intervention, Control, Outcomes, and Study design (PICOS) was used to formulate the eligibility criteria, which consisted of individuals of both sexes, aged between 18 and 64 years, and diagnosed with migraine with or without aura.[1]

Regarding the intervention, we included studies that conducted supervised and monitored running (street or treadmill) for at least six weeks and compared it with a control group (no aerobic exercise or other aerobic exercises [e.g., walking, dancing, or cycling]). Aerobic exercise was considered if performed using a training intensity between 60% and 90% of maximum heart rate (HRmax).[20,33,34]

The outcomes assessed were migraine frequency and intensity (days/month), measured using a headache diary and the visual analog scale, respectively. Randomized and quasi-randomized controlled trials were included. Studies without a comparison or control group, with any other type of associated headache, or conducted with pregnant women or para-athletes were excluded.

Search strategy

The search was conducted in the following databases from September 2021 to November 2021: BVS, MEDLINE/PubMed, Cochrane, CINAHL, Embase, SCOPUS, and Web of Science; the grey literature was also included (Google Scholar e ClinicalTrials.gov). The descriptors were combined using Boolean operators (OR and AND), and no language or publication date restrictions were applied. The search strategy is shown in Table 1.

Table 1. Search strategy

Database	Descriptors and Boolean operators
MEDLINE (Pub-Med)	("Migraine Disorders" OR "Headache" OR "Migraine") AND ("Running") AND ("Walking" OR "Dancing" OR "Bicycling" OR "Cycling" OR "Exercise")
BVS	("Transtornos de Enxaqueca" OR "Migraine Disorders" OR "Trastornos Migrañosos" OR "migraines" OR "Cefaleia Enxaquecosa" OR "Estado de Mal Enxaquecoso" OR "Síndromes Enxaquecosas" OR "Síndromes de Enxaqueca" OR "Transtornos da Enxaqueca" OR "cefaleia" OR "headache" OR "cefalea" OR "céphalée" OR "cefalgia" OR "Dor de Cabeça" OR "migrânea" OR "migraine") AND ("corrida" OR "running" OR "carrera" OR "Course à pied") AND ("Caminhada" OR "walking" OR "caminata" OR "Marche à pied" OR "dança" OR "dancing" OR "baile" OR "danse" OR "ciclismo" OR "bicycling" OR "cycling" OR "ciclismo" OR "cyclisme" OR "Exercício Físico" OR "exercise" OR "Ejercicio Físico" OR "Exercice physique")
Cochrane Central Register of Controlled Trials	("Migraine Disorders" OR "Headache" OR "Migraine") AND ("Running") AND ("Walking" OR "Dancing" OR "Bicycling" OR "Cycling" OR "Exercise")
CINAHL	("Migraine Disorders" OR "Headache" OR "Migraine") AND ("Running") AND ("Walking" OR "Dancing" OR "Bicycling" OR "Cycling" OR "Exercise")
Embase	("Migraine" or "headache") and ("running") and ("walking" or "dancing" or "cycling" or "exercise")
Scopus	("Migraine Disorders" OR "Headache" OR "Migraine") AND ("Running") AND ("Walking" OR "Dancing" OR "Bicycling" OR "Cycling" OR "Exercise")
Web of Science	("Migraine Disorders" OR "Headache" OR "Migraine") AND ("Running") AND ("Walking" OR "Dancing" OR "Bicycling" OR "Cycling" OR "Exercise")

Two authors (CBT and DAO) independently searched for studies by accessing and identifying titles and abstracts according to eligibility criteria. In case of doubt, the studies were removed for further full-text analysis. All results were compared between authors during a consensus meeting, and a third author (MMMBB) was requested in case of disagreement.

Data extraction

The authors read and analyzed the titles of all studies, followed by duplicate removal using the Mendeley software (Mendeley, version 1.17.4, Elsevier, New York, USA). The full text of the selected studies was also read in detail, according to eligibility criteria. The following data were extracted from studies and tabulated in an Excel sheet: identification number, authors, title, database, year of publication, and inclusion or exclusion criteria. From studies selected for full-text reading, we extracted the study design; type of migraine; recruitment procedure; the number of participants; sex; age; mean ± standard deviation of the frequency and intensity of migraine (days/month) of experimental and control groups; type, duration, and frequency of physical exercise; intervention protocol; clinical data before and after the intervention; group types; adverse effects; type of randomization; allocation concealment; type of concealment; blinding of participants and personnel; and selective outcome reporting.

Quality of assessment

The risk of bias was assessed in pairs using the Cochrane collaboration tool for assessing the risk of bias during a consensus meeting among authors. The analysis included seven 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 outcome reporting (reporting bias), and other biases.[35]

Qualitative and quantitative data analysis

Two authors (CBT and DAO) assessed the methodological quality of each study using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2.0 tool).[36]

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) assessed the strength of recommendation and the certainty of evidence (high, moderate, low, or very low) according to methodology, consistency, accuracy of results, and publication bias.[35,36]

The following data were presented in graphs: (1) frequency of migraine attacks – subgroup of interval running vs. control; (2) frequency of migraine attacks – subgroup of continuous running vs. control; (3) pain intensity – continuous running vs. control.

For the quantitative analysis, a meta-analysis was conducted and presented in a forest plot using the mean difference (MD), adjusted for a random effect, and 95% confidence intervals (95% CI). Heterogeneity was assessed using I2 statistics and interpreted as low (25%), moderate (50%), or high (75%).[35-37]

Results

Study selection

A total of 483 articles were obtained (477 from electronic databases and 6 from grey literature). After duplicate removal, 286 studies were selected for title reading; a total of 270 studies were excluded in this stage, leaving 16 studies for abstract reading. Seven studies were excluded for not meeting the eligibility criteria. Nine studies were selected for full-text reading; of these, seven were excluded. Therefore, two studies were included for the qualitative and quantitative analyses.[37,38] Figure 1 shows the description of the studies selected.
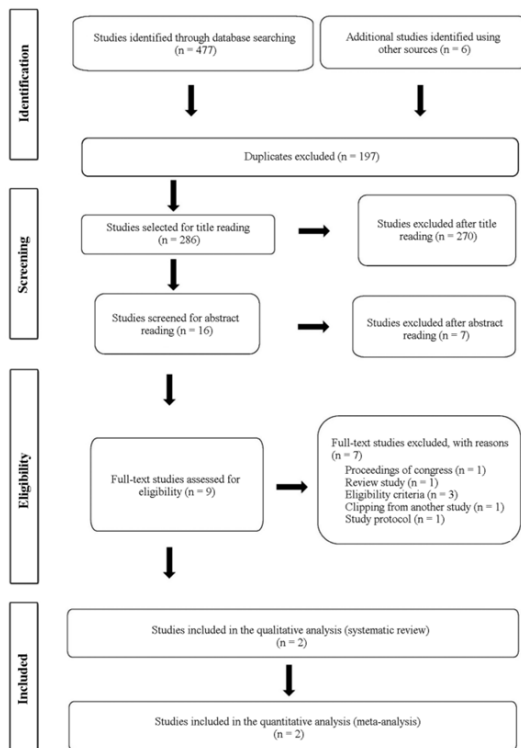
Figure 1. Flowchart of study selection based on PRISMA model

Study characteristics

A total of 52 individuals (42 females and 10 males) aged between 18 and 52 years were included. The diagnosis of migraine was established in the included studies[37,39] by a neurologist, according to the IHS criteria.[1] Individuals had episodic migraine with and without aura. One study[37] was conducted in a university hospital in Germany, while the other[40] in a university hospital in Switzerland. Regarding recruitment, both studies conducted newspaper advertisements; Darabaneanu et al.[39] recruited 30 individuals from September to December 2008, whereas Hanssen et al.[40] recruited 45 individuals from May 2014 to April 2017.

Interventions

Both studies[37,39] reported a previous exercise test to ensure aerobic training with moderate intensity. Darabaneanu et al.[39] used the physical working capacity protocol on a treadmill, while Hanssen et al.[40] applied the treadmill ergospirometry as exercise stress testing.

Darabaneanu et al.[39] randomized individuals into two groups: continuous running on a treadmill (10 minutes of warm-up, 30 minutes with HRmax between 60% and 75%, and 10 minutes of cool-down) and daily routine without modifications (control group). The continuous running activity was conducted three times per week (two were

supervised).

Hanssen et al.[40] applied two aerobic training intensities and randomized individuals into three groups: supervised continuous running on a treadmill (45 minutes at 70% of HRmax), supervised interval running on a treadmill (45 minutes alternating between 90% and 95%, followed by a resting period at 70% of HRmax), and daily routines without modifications (control group). Hanssen et al.[40] measured heart rate during the training period to certify that individuals performed the running at the aerobic threshold. However, it was not clear whether Darabaneanu et al.[39] had the same precaution.

Regarding the intervention duration, the study of Darabaneanu et al.[39] and Hanssen et al.[39] submitted individuals to 10 and 12 weeks of training, respectively. This training was performed three [37] or two[39] times a week.

Running was not compared with other aerobic exercises (*e.g.*, walking, dancing, or cycling) due to a lack of studies including this comparison.

Outcomes

The frequency of migraine attacks was assessed in two studies[38,39] using the headache diary. Individuals filled diaries at baseline (i.e., four and eight weeks before training),[38,39] during training, and the end of the study. A follow-up assessment was also conducted 10 days[38] and 8 weeks[39] after the intervention. Regarding the intensity of migraine attacks, only Darabaneanu et al.[39] assessed it using the visual analog scale (0 corresponding to the lowest and 10 to the highest intensity), demonstrating an MD of 0.10 hours/month after the intervention.

As for the secondary outcome, Darabaneanu et al.[39] assessed the effects of running on quality of life and stress improvement. Hanssen et al.[40] assessed retinal vessel diameters in response to exercise as a biomarker of cardiovascular risk.

Adverse effects

Both studies did not report adverse effects in the intervention and control groups.

Synthesis of results

A summary of the characteristics, training parameters and results of the included studies[37,39] is presented in Table 2. The risk of bias in the selected studies is shown in Table 3. Each domain was automatically categorized into a risk of bias summary (Figure 2) and graph (Figure 3) with colors and symbols.

Table 2. Characteristics, prescription parameters, and results of the included studies

Citation Country Study design	Migraine type (n)	Group (n) Sex Age (mean)	Treatment period	Type, duration, and frequency of the activity	Protocol	Results
Darabaneanu et al.[39] Germany RCT	Migraine with and without aura ICHD-II (n = 16)	G1 Ex (n = 8) 2M/6F 37.8 (8.9); G2 CON (n = 8) 1M/7F 34.1 (16.5)	8-week baseline 10-week intervention 8-week FU; 8-week baseline 10-week observation 8-week FU	Aerobic treadmill running 50 min, 3x/week; No physical activity	10 min warm-up, 30 min jogging between 60% to 75% of HRmax, and 10 min cool-down; Routine activities	The frequency and intensity of migraine were not different between groups.
Hanssen et al.[40] Switzerland RCT	Migraine without aura ICHD-II (n = 36)	G1 HIIT (n = 13) 3M/10F 36.2 (10.7); G2 MCT (n = 11) 2M/9F 37.0 (8.7); G3 CON (n = 12) 2M/10F 37.3 (11.9)	4-week baseline 12-week intervention 10 days FU	Interval running 45 min, 2x/week; Continuous running 45 min, 2x/week; No physical activity	400 m warm-up, 4 x 4 min (intensive run) between 90 and 95% of HRmax, 4 x 3 min active rest at 70% of HRmax; Continuous running at 70% of HRmax; Routine activities	A moderate interaction was found in reducing the frequency of migraine ($\eta^2_p = 0.12$), favouring interval running over continuous running and control groups.

CON = control group; Ex = exercise; F = female; FU = follow-up; G1 = group 1; G2 = group 2; G3 = group 3; HIIT = high-intensity interval training; HR_{max} = maximum heart rate; ICHD = International Classification of Headache Disorders; M = male; MCT = moderate continuous aerobic training; min = minutes; n=number of individuals; RCT = randomized controlled trial; η^2_p = "partial eta squared".

Table 3. Risk of individual bias

Authors	Inclusion of neurological diagnosis by ICHD	Standard randomization	Type of randomization	Allocation concealment	Type of concealment	Blinding of participants	Blinding of personnel	Blinding of outcome evaluator	Intention to treat analysis	Selective outcome reporting	Study design	Analysis	Clinical scales	Prior exercise testing	Psych. tests
Darabaneanu et al.[39]	Yes	No	Stratified by age, sex, and migraine days; to 1:1: EX and CON.	No	ND	ND	No	No	No	No	ECR-Pilot	ANOVA	Headache diary and VAS	PWC 150	(BDI); (BL); (SVF); (FPI)
Hanssen et al.[40]	Yes	No	Stratified by age, sex, BMI, level of physical activity, migraine days, and VO2max; to 1:1:1: HIIT, MCT, or CON	Yes	ND	ND	Yes	Yes	No	No	ECR	K-S and Levene rANOVA	Headache diary	(PAR-Q) and (CPET) on a treadmill	No

BDI = Beck Depression Inventory; B-L = "Beschwerdeliste"; BMI = body mass index; CON = control; CPET = cardiopulmonary stress test; EX = exercise; FPI = "Freiburger-Persönlichkeits-Invent"; HIIT = high intensity interval training; KS = Kolmogorov-Smirnov; MCT = moderate continuous aerobic training; ND = Not described; PWC 150 = physical working capacity; PAR-Q = Physical Activity Readiness Questionnaire; rANOVA = analysis of variance; RCT = randomized controlled trial; SVF = "Stress Verarbeitungs-Fragebogen"; SPSS = Statistical Package for Social Science; VAS = Visual Analog Scale; VO2max = maximal oxygen uptake
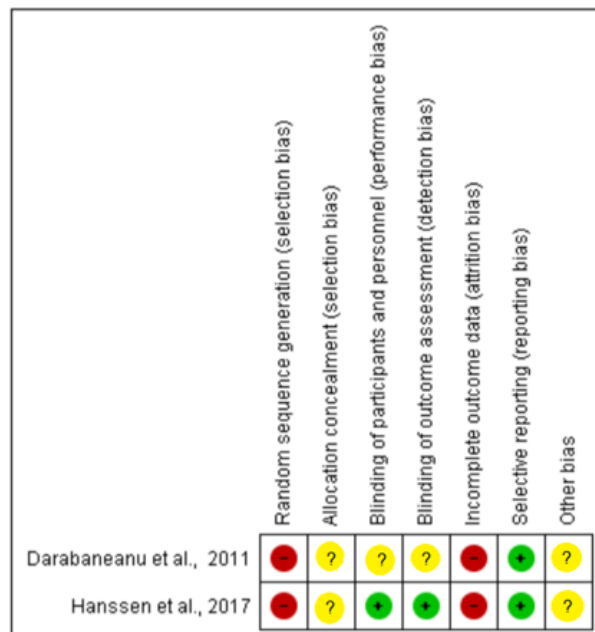
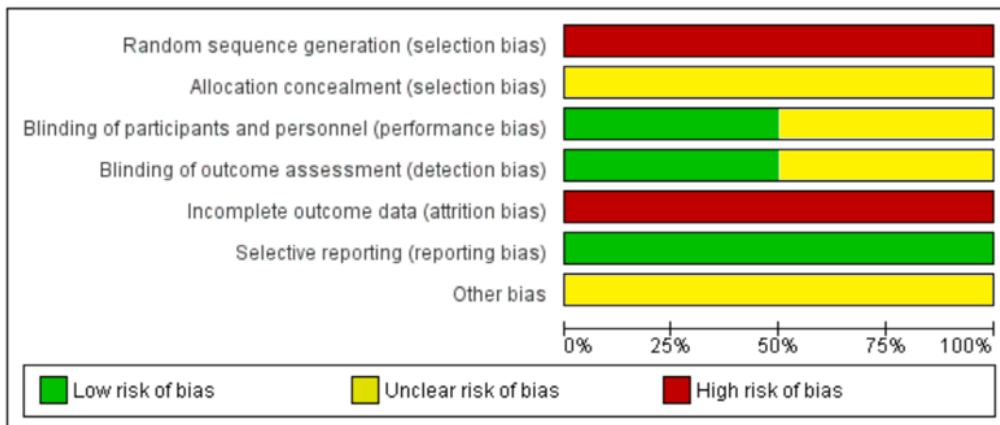**Figure 2.** Risk of bias summary: judgments of authors about each risk of bias item.

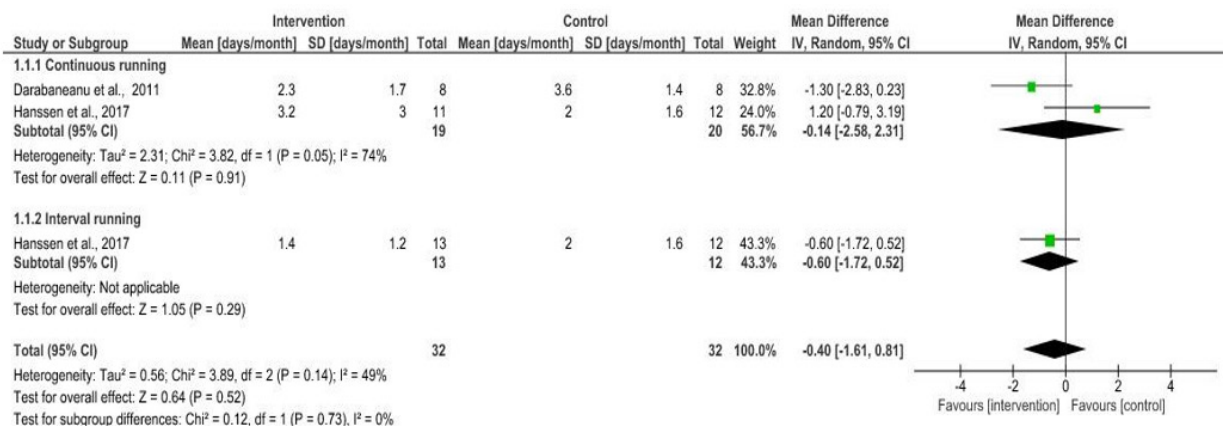**Figure 3.** Risk of bias graph: judgments of authors about each risk of bias item.

Figure 4. Forest plot for the frequency of migraine.

Running compared to control for treatment of adults with migraine

Patient or population: adults with migraine
Setting: Control: other aerobic exercise (walking, dancing, or cycling) or no exercise. Outcome: Frequency and intensity of migraine.
Intervention: Running
Comparison: control

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	**Risk difference with Running**
Pain frequency (days/month) Continuous running (MCT and Jogging) assessed with: headache diary follow-up: mean 10-12 weeks	39 (2 RCTs)	⊕◯◯◯ Very low[a,b,c,d,e,f,g,h]	-	The mean pain frequency (days/month) Continuous running was **0** days/month	MD **0.14 days/month lower** (2.58 lower to 2.31 higher)
Pain frequency (days/month) Interval running (HIIT) (Interval running) assessed with: headache diary follow-up: mean 12 weeks	25 (1 RCT)	⊕◯◯◯ Very low[b,e,f,g,i]	-	The mean pain frequency (days/month) Interval running (HIIT) was **0** days/month	MD **0.6 days/month lower** (1.72 lower to 0.52 higher)
Pain intensity (days/month) (VAS) assessed with: Headache Diary (Visual Analog Pain Scale) follow-up: mean 10 weeks	16 (1 RCT)	⊕◯◯◯ Very low[a,b,e,f,g]	-	The mean pain intensity (days/month) was **0** days/month	MD **0.1 days/month higher** (0.17 lower to 0.37 higher)

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. risks of selection and performance bias
b. patient losses during the study
c. different follow up
d. interventions with different protocols
e. CI crosses the null line
f. n very low
g. small sample size, large IC
h. No regular distribution at baseline
i. risk of selection bias

Figure 5. Summary of the results of certainty of the evidence.

Meta-analysis

We conducted overall (running vs. control) and subgroup analyses (continuous running vs. control [no intervention]; interval running vs. control [no intervention]) (Figure 4). None of the studies showed a significant effect of running in reducing migraine frequency (-0.40 [95%CI = -1.61 to 0.81]). The intensity outcome was not analyzed because it was assessed in one study.[39] Last, heterogeneity between studies was moderate (I^2 = 49%).

Qualitative analysis

Figure 5 shows the results regarding the certainty of the evidence for the frequency and intensity of migraine attacks. Despite being randomized clinical trials, studies[37,39] presented a very low certainty of evidence and weak strength of recommendation.

Discussion

The studies included in this review[37,39] showed that running decreased migraine frequency during treatment. Darabaneanu et al.[39] demonstrated the effects of continuous running on migraine. Hanssen et al.[40] showed a moderate reduction in the frequency of migraine (η^2_p = 0.12), favouring interval running over continuous running and controls. Although both studies[37,39] showed that running (continuous or interval) decreased the frequency of migraine, the biases observed overestimated the findings and reduced the certainty of evidence.

Controlling the frequency of migraine attacks is clinically

important because it helps monitor the therapeutic success and improve the quality of life, including the personal, family, social, and productive aspects of the individual.[40] Although acute or prophylactic drug treatment is still considered the gold standard for managing migraine attacks, non-pharmacological treatment has been increasingly recognized as an adjunct or sole treatment option.[41] Running may be a non-pharmacological, low-cost, and easy-to-implement option.[40] However, data regarding the frequency of migraine attacks depends on the minimal clinically important difference. The literature establishes that individuals with the number of migraine days reduced by at least 50% are considered responders or present a standard of efficacy for drug treatment.[42] In clinical trials, randomization reduces selection bias by decreasing the likelihood that groups will differ significantly at baseline; thus, influencing the outcome. The included studies[37,39] did not properly perform the randomization and allocation concealment.[43] Furthermore, the absence of appropriate allocation concealment overestimates the effect size of the intervention by up to 30%.[44]

Individuals from the included studies[37,39] were not blinded because of the difficulty in elaborating a placebo for aerobic training, resulting in performance bias and overestimating the results.[18] The blinding of evaluators and examiners is essential to avoid classification bias and measurement errors (detection bias), preventing the individual or caregiver from interfering with results (performance bias). Only Hanssen et al.[40] blinded the evaluators and examiners.

The studies[37,39] failed to conduct the loss to follow-up. The authors neither inform how they dealt with these losses nor performed an intention-to-treat analysis, indicating attrition bias and possibly generating other biases. Also, excluding these patients from the analysis may have overestimated the results of the intervention. The loss to follow-up recorded in the studies was 20%[40] and 46.67%.[36]

The sample size calculation predicts the power of a study, and samples smaller than necessary may not generate reliable results.[18] Thereby, inadequate sample sizes and large confidence intervals contributed to classifying the certainty of evidence as very low. In addition, only Hanssen et al.[40] calculated the sample size using the main outcome. Darabaneanu et al.[39] used intragroup comparisons, compromising the reliability of the results. The studies[39,40] conducted different training protocols and reported the primary and secondary outcomes. Therefore, no reporting or publication bias was observed.

Darabaneanu et al.[39] applied 30-minute aerobic training three times a week for 10 weeks, with intensity from 60% to 75% of HRmax. Hanssen et al.[40] applied 45-minute aerobic training twice a week for 12 weeks, with intensity from 90% to 95% of HRmax. No difference was observed in the duration and frequency of the intervention (in weeks).

According to the ACSM, the frequency of continuous aerobic exercise should vary from three to five times a week, with intensity varying from 60% to 90% of HRmax, and duration from 20 to 60 minutes. The included studies[37,39] were in line with ACSM recommendations, except for the training frequency conducted by Hanssen et al.[40], which was performed twice a week.

The authors of the included studies[37,39] were cautious regarding the assessed parameters, description of the follow-up, and inclusion of effort tests before interventions. They also conducted the follow-up and the same assessments pre-and post-intervention.[37,39] The very low certainty of evidence showed that running did not affect the frequency of migraine attacks compared with the control group. In addition, the benefits, harms, and adverse effects were inconclusive since authors did not report these data.[37,39] Darabaneanu et al.[39] did not perform the follow-up properly since the protocol was unsupervised once a week and performed at home. For instance, it was not possible to determine whether these patients performed aerobic training at home with an intensity between 60% and 75% of HRmax.

We did not analyze the intensity of migraine attacks because only Darabaneanu et al.[39] reported these results. Given the very low certainty of the evidence, data are not sufficient to recommend running as an effective treatment for reducing the frequency and intensity of migraine attacks.

Conclusion

Clinical trials with good methodological quality on the topic were scarce. Only two studies were included in the qualitative and quantitative analyses of this review. They presented a high risk of bias and very low certainty of evidence. The results regarding aerobic training were insufficient to reduce migraine attacks (frequency and intensity) compared with other or no aerobic exercise.

Perspective
The decision-making in migraine treatment depends on the preferences of individuals, the accessibility of high-cost drugs, and professional experience. Drug treatment

is considered a gold standard, but non-pharmacological treatments have been well accepted due to their effectiveness.[45] Nevertheless, the evidence that running reduces migraine attacks remains unclear.

Future studies

The main reason for developing systematic reviews is to find scientific evidence to guide clinical practice. When well designed and conducted, clinical trials suggest new protocols or changes in the existing protocols. Therefore, new clinical trials with better methodological quality and control of internal and external variables are needed to evaluate running as an alternative intervention for treating migraine.

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Conflicts of interest

The authors declare no conflicts of interest.

Author contribution

CBT, DAO, independently screened and reviewed titles and abstracts to identify the eligible studies; CBT, DAO, MMMBB, assessed full-text articles for eligibility; CBT, conducted the meta-analysis; CBT, DAO, independently performed data extraction and quality assessment for the studies included in the meta-analysis. All authors contributed to the writing of the manuscript. All authors read and approved the final manuscript.

Data availability statement

The datasets used and analyzed during the study are available from the corresponding author upon reasonable request.

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