Review Article

Effect of Aerobic Training on Homocysteine and Lipid Profiles in Adults: A Systematic Review and Meta-Analysis

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Aerobic exercise, Cardiovascular diseases, Homocysteine, Lipid profile,

ABSTRACT

Aims A sedentary lifestyle, which is a known risk factor for several diseases, including cardiovascular disorders, is associated with elevated homocysteine levels. Studies have demonstrated that physical training can influence homocysteine levels in the body. The present study aimed to investigate the effect of aerobic exercise on homocysteine and lipid profiles in adults.

Materials & Methods A systematic search of English and Persian articles published in PubMed, Web of Science (WOS), Scopus, Scientific Information Database (SID), Noor Mags, and Magiran databases was conducted up to June 2024. The mean difference and 95% confidence intervals (CIs) were calculated using a random-effects model. Heterogeneity was assessed using the I^2 statistic, and publication bias was evaluated through visual inspection of the funnel plot and Egger's test.

Findings A total of 19 studies comprising 511 adults were included in this meta-analysis. The results indicated that aerobic exercise significantly reduced homocysteine levels [WMD= -0.915, 95% CI: -1.427 to -0.403, P= 0.001], LDL [WMD= -8.934 mg/dL, 95% CI: -13.555 to -4.314, P= 0.001] and total cholesterol (TC) [WMD= -7.390 mg/dL, 95% CI: -13.881 to -0.900, P= 0.026] compared to control groups. However, no significant changes were observed in triglycerides (TG) [WMD= -3.418 mg/dL, 95% CI: -9.466 to 2.611, P= 0.266] and high-density lipoprotein (HDL) [WMD= 1.940 mg/dL, 95% CI: -0.920 to 4.799, P= 0.148].

Conclusion This meta-analysis suggests that aerobic exercise in adults is associated with reduced levels of homocysteine, total cholesterol, and low-density lipoprotein (LDL). Therefore, it can be recommended as a practical and non-pharmacological strategy to help prevent cardiovascular disease and diabetes.

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مقاله مروری

تاثیر تمرینات هوازی بر هموسیستئین و پروفایل لیپیدی در بزرگسالان: مرور نظام‌مند و فراتحلیل

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چکیده

هدف سبک زندگی کم‌تحرک با افزایش سطح هموسیستئین در ارتباط است که یکی از عوامل خطر شناخته‌شده برای بسیاری از بیماری‌ها، از جمله بیماری‌های قلبی‌عروقی محسوب می‌شود. مطالعات نشان داده‌اند که فعالیت بدنی می‌تواند بر سطح هموسیستئین در بدن تأثیرگذار باشد. هدف از این مطالعه، بررسی اثر تمرینات هوازی بر سطح هموسیستئین و پروفایل لیپیدی در بزرگسالان بود.

مواد و روش‌ها: جستجوی سیستماتیک مقالات فارسی و انگلیسی منتشرشده در پایگاه‌های اطلاعاتی PubMed، Web of Science، Scopus، SID، Noor Mags و Magiran تا ژوئن ۲۰۲۴ انجام شد. اختلاف میانگین و فاصله اطمینان ۹۵٪ با استفاده از مدل اثرات تصادفی محاسبه گردید. ناهمگنی مطالعات با استفاده از آزمون آماری I^2 بررسی شد و سوگیری انتشار با تحلیل بصری نمودار فونل پلات و آزمون Egger ارزیابی گردید.

یافته‌ها: در مجموع ۱۹ مطالعه و ۵۱۱ آزمودنی بزرگسال وارد فراتحلیل حاضر شدند. نتایج نشان داد که تمرین هوازی سبب کاهش معنادار هموسیستئین [WMD=-۰/۹۱۵ (-۱/۴۲۷ الی -۰/۴۰۳)، P=۰/۰۰۱]، LDL [WMD=-۸/۹۳۴ mg/dL (-۱۳/۵۵۵ الی -۴/۳۱۴)، P=۰/۰۰۱] و TC [WMD=-۷/۳۹۰ mg/dL (-۱۳/۸۸۱ الی -۰/۹۰۰)، P=۰/۰۲۶] نسبت به گروه کنترل در بزرگسالان شد. اما تمرین هوازی سبب تغییر معنادار TG [WMD=-۳/۴۱۸ mg/dL (-۹/۴۴۶ الی ۲/۶۱۱)، P=۰/۲۶۶] و HDL [WMD=۱/۹۴۰ mg/dL (-۰/۹۲۰ الی ۴/۷۹۹)، P=۰/۱۸۴] نسبت به گروه کنترل در بزرگسالان نشد.

نتیجه‌گیری: نتایج فراتحلیل حاضر نشان داد که تمرین هوازی در بزرگسالان سبب کاهش معنادار هموسیستئین، TC و LDL سرمی می‌شود و بنابراین می‌تواند به عنوان یک راهکار غیردارویی و کاربردی برای کاهش بیماری‌های قلبی - عروقی و دیابت به افراد پیشنهاد شود.

کلیدواژه‌ها:
تمرین هوازی
هموسیستئین
پروفایل لیپیدی
بیماری های قلبی عروقی

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Introduction

Obesity is caused by environmental and genetic factors and can be considered a serious condition associated with cardiovascular problems [1]. Nowadays, cardiovascular disease is recognized as one of the leading causes of death in the world, and many factors are involved in the development of this disease. The most important risk factors for these diseases include insulin resistance, high waist-to-hip ratio [2], low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) [3] and high-density lipoprotein (HDL) [4], total cholesterol (TC), triglycerides (TG) [5], lipid disorders and their oxidation, inappropriate dietary concentrations, inactivity, obesity, smoking, high blood pressure, and increased homocysteine levels [3, 4, 6].

Homocysteine is an amino acid in the blood that is formed from the demethylation of methionine and is known as a homologue of cysteine. Epidemiological studies have indicated that high levels of homocysteine in blood plasma are a risk factor for coronary artery disease, heart attack, and peripheral vascular disease, and cause atherosclerosis in three ways: 1) damage to the inner wall of the arteries, 2) interference with the work of blood clotting factors, 3) oxidation of LDL [7]. The reduction of homocysteine levels decreases the risk of heart attacks and strokes [8]. Plasma homocysteine levels increase with age, which has been shown to be more common in women [9]. Factors contributing to higher total homocysteine concentrations in adults include low serum folate concentrations and an increased prevalence of vitamin B12 deficiency as a result of malabsorption of these vitamins from the intestines in adults [10]. Many studies have revealed that the association between homocysteine levels and atherosclerosis is even stronger than the association between atherosclerosis and cholesterol. On the other hand, increased homocysteine concentrations are themselves an independent risk factor for coronary artery disease [11].

Nowadays, the positive effects of exercise and physical activity for the primary and secondary prevention of cardiovascular diseases have been well established. Exercise and physical activity are generally associated with a healthy lifestyle [12]. Physical activity improves homocysteine and several biochemical variables that can affect the homocysteine metabolism pathway. Oxidative stress may play a more critical role in this regard. Several studies investigating the effect of physical activity on cardiovascular risk factors support the use of aerobic activities, such as light jogging, mountain climbing, long-distance walking, and swimming. The results of these studies show that aerobic exercise reduces plasma homocysteine levels [13, 14]. In a meta-analysis, researchers examined the effect of aerobic exercise alone in 22 studies involving 520 subjects and reported that aerobic exercise increased plasma homocysteine levels [15]. On the other hand, Silva et al. (2020) reviewed a systematic review of 22 studies and reported that exercise training increases plasma homocysteine levels [16].

Elevated homocysteine levels, especially in individuals with a sedentary lifestyle, are known to be a risk factor for chronic diseases, including cardiovascular disease, type 2 diabetes, and cognitive impairment. Moreover, lipid profile abnormalities, such as increased LDL and TG, and decreased HDL, are directly associated with the risk of atherosclerosis and metabolic syndrome. Studies have shown that physical activity, particularly aerobic exercise, can play a significant role in modulating these indicators [17].

Several physiological mechanisms have been proposed to explain the beneficial effects of aerobic exercise on blood homocysteine and lipid levels. In the context of homocysteine, regular aerobic exercise may reduce homocysteine levels by reducing oxidative stress, increasing antioxidant capacity, expanding the remethylation of homocysteine to methionine through pathways dependent on vitamins B6, B12, and folate, and increasing the metabolic utilization of methionine [15]. On the other hand, aerobic exercise can reduce TG, LDL, and TC and increase HDL by stimulating the secretion of epinephrine and norepinephrine, activating lipoprotein lipase, increasing enzymes involved in lipid metabolism such as LCAT, and improving reverse cholesterol transport. In addition, increasing the utilization of fatty acids by muscles during regular exercise is another pathway modulating plasma lipids [18].

Given the conflicting findings in previous studies and differences in design, type of exercise, intensity, and duration of intervention, a meta-analysis seems necessary to investigate the effect of aerobic exercise on homocysteine levels and lipid profiles in adults. The present study aimed to systematically analyze the available evidence and provide an overall estimate of the effectiveness of aerobic exercise on these metabolic indicators in adults.

Materials and Methods

The present study is a systematic review and meta-analysis conducted according to the Cochrane and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [19, 20].

Data Sources and Search Methods

A search was conducted in databases to retrieve relevant research articles. To this end, Scopus, PubMed, and Web of Science (WOS) databases were searched for English-language articles up to June 2024 (without limiting the year of publication) using the following keywords:

"Aerobic Exercise", "HIIT", "Interval training", "Aerobic Interval Training", "Aerobic Interval", "Intermittent Training", "High Intensity Intermittent", "High Intensity Interval Exercise", "High Intensity", "High Intensity Interval Training", "Sprint Interval Exercise", "SIT", "Moderate-Intensity Continuous Exercise", "Homocysteine", "Lipid profile", "serum lipids", "Lipid profile", "Adults".

In addition, a search was conducted in the Scientific Information Database (SID) and Magiran databases for Persian articles up to June 2024 using the following keywords (in Persian):

"aerobic exercise", "interval exercise", "aerobic interval training", "interval training", "high-intensity interval training", "sprint interval training", "moderate-intensity interval training", "moderate-intensity continuous exercise", "homocysteine", "lipid profile", "serum lipids", "lipid profile", and "adults."

Then, the reference lists of the retrieved articles and the articles citing them were manually reviewed in Google Scholar. The database searches were conducted independently by two researchers.

Inclusion and Exclusion Criteria

To conduct the meta-analysis, articles with the following characteristics were included in the study: 1) Randomized clinical trials (RCT) and non-randomized studies (NRS), published in Persian or English; 2) studies conducted on adults; 3) studies investigating the effect of aerobic exercise versus a control group; 4) studies measuring homocysteine and lipid profile (TC, TG, HDL, LDL); 5) those studies that included mean and standard deviation data for the post-test and pre-test of the variables mentioned above for subjects of both groups (aerobic exercise and control). Exclusion criteria involved animal studies, abstracts of articles presented at conferences, theses, cross-sectional studies, reviews, and meta-analyses. The initial evaluation of the articles was conducted independently by both researchers.

Data Extraction

Information on study type, first author, year of publication, randomization or non-randomization, sample size, subject characteristics including age, gender, and exercise protocol (type of intervention, length of intervention, number of sessions per week, and exercise intensity) was extracted [21-24]. If there was insufficient data to perform the meta-analysis, the corresponding author was contacted via email, and the data required for the present meta-analysis were obtained. Moreover, if the corresponding author did not respond or did not receive the article, data were extracted from the article chart using the Get Data software [21-24].

Quality Assessment of Articles

The quality of studies was assessed using Pedro's 9-question checklist [21-24]. The evaluation criteria included the following: 1) clarity of the eligibility criteria for subjects, 2) random assignment of participants to different groups, 3) participants to be not familiar with their groupings, 4) similarity of the subjects in terms of body weight in different study groups, 5) blind assessment for the primary research variable (blinding of all assessors), 6) dropping out of less than 15% of participants of the study, 7) intention to treat analysis, 8) reporting of statistical differences between groups for the primary research variable, 9) reporting of the mean, standard deviation, and significance level (P-value). All questions on Pedro's checklist were answered with two options: yes ✓ or no ×. The minimum score was zero, and the maximum was 9, where a higher numerical value indicated a higher quality of the study.

Meta-analysis

The present meta-analysis study was conducted to compare the effect of aerobic exercise on homocysteine and lipid profiles in adults. In this study, mean, standard deviation, and sample size were employed for statistical analysis. Data analysis was calculated using a random-effects model, and the mean difference and 95% confidence interval were considered. To determine the heterogeneity of studies, the (I^2) test was used; according to the Cochrane guidelines, heterogeneity was interpreted as less than 25% = mild heterogeneity, 25-50% = low heterogeneity, 50-75% = moderate heterogeneity, and higher than 75% = high heterogeneity [21-24]. It is worth noting that a random-effects model was employed to analyze the data. In the absence of heterogeneity, sensitivity analysis was performed using the leave-one-out method with (I^2) less than 25 as the criterion. Publication bias was also assessed using a visual interpretation of the Funnel Plot. If bias was observed, Egger's test was used as a secondary deterministic test, with a significance level of 0.1 considered significant for publication bias [25]. Statistical analysis tests were performed using CMA (version 2.0) software [25].

Results

Based on a search in scientific databases up to June 2024, 182 articles were found. After removing 85 duplicate articles and screening the titles and abstracts of the remaining articles, 43 were finally selected for full-text evaluation. After screening the full text of the articles, 24 articles were excluded from the present meta-analysis due to the lack of post-test data, insufficient research variables, or the absence of a control group [43, 44]. Finally, 19 studies were included in the present meta-analysis. Therefore, there were 19, 7, 7, 7, and 7 studies for the homocysteine, TG, TC, HDL, and LDL variables, in respective order.

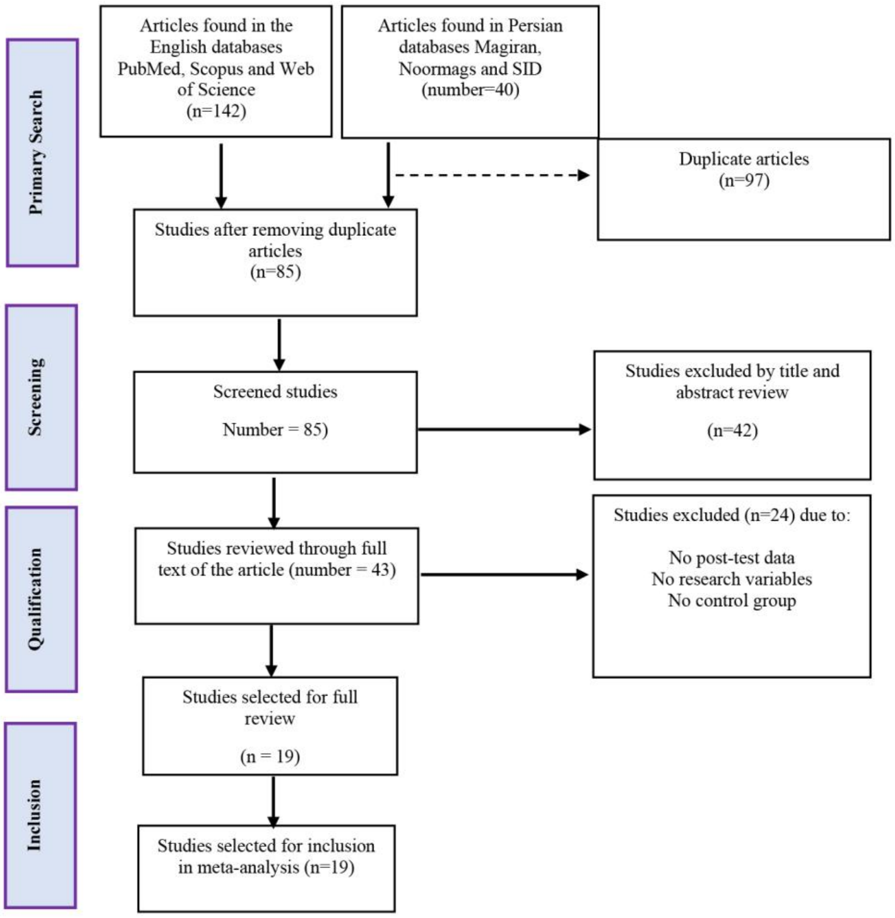

Figure 1. Study selection flowchart

Table 1. Characteristics of subjects and exercise protocol

Exercise intensity (%)	Workout duration (min)	Length of intervention in weeks (Number of sessions per week)	Body mass index (kg/m)	Age (Year)	Variables	Characteristics of the subjects	Sample (Gender)	Study Type-Country	Ref.
Running training at an intensity of 50% to 100% of maximum aerobic speed	-	8 (3)	Exercise: 29.50±4.50 Control: 31.40±2.60	HIIT Exercise (14 people): 24.20±4.80 Control (14 people): 22.90±5.30	Homocysteine TC TG HDL LDL	Polycystic ovary syndrome	28 females	RCT – Iran	Mohammadi et al. 2023 [26]
Continuous running training at an intensity of 65% to 75% of maximum heart rate	20 to 35	8 (3)	Exercise: 30.20±3.90 Control: 28.80±4.51	Exercise (15 people): 46.60±5.83 Control (15 people): 45.50±8.12	Homocysteine	Non-athlete	30 females	RCT – Iran	Porsesh et al. 2022 [27]
Treadmill running	20 to 35	8 (3)	HIIT training:	HIIT Exercise (11 people):	Homocysteine	Cardiovascular patients	32 males and	RCT – Iran	Avazpour et al. 2021

Exercise intensity (%)	Workout duration (min)	Length of intervention in weeks (Number of sessions per week)	Body mass index (kg/m)	Age (Year)	Variables	Characteristics of the subjects	Sample (Gender)	Study Type-Country	Ref.
training at an intensity of 70% to 100% VO2peak with an activity-to-rest ratio of 15 s to 1 min			28.30±1.40 Control: 28.70±2.10	54.60±3.70 Control (11 people): 57.80±3.40			females		[28]
Walking exercise at an intensity of 60% to 70% of maximum heart rate	75	16 (2)	Exercise: 27.21±4.32 Control: 28.74±4.40	Exercise (15 people): 69.68±11.30 Control (18 people): 67.61±6.00	Homocysteine TC TG HDL LDL	Type 2 diabetes	33 females	RCT – Brazil	Silva et al 2020 [29]
Exercise bike workout: Ten 1-minute intervals at an intensity of 85% to 90% of maximum heart rate and 1 min recovery at an intensity of 50% to 55% of maximum heart rate	20	8 (3)	Exercise: 32.10±1.93 Control: 31.42±2.61	Exercise (15 people): 23.94±3.14 Control (15 people): 23.18±2.36	Homocysteine HDL LDL	Overweight and obese	30 males	RCT – Iran	Mohammadyari et al 2018 [13]
Aerobic exercise at an intensity of 65% to 75% of maximum heart rate	55 to 60	8 (3)	Exercise: 31.00±5.98 Control: 31.65±5.75	Exercise (20 people): 32.00±1.05 Control (20 people): 31.00±8.67	Homocysteine TC TG HDL LDL	Obese	40 females	RCT-Iran	Tofighi et al. 2017 [30]
Pedalling exercise with an electric bike at an intensity of 40% to 70% of maximum heart rate reserve	30	8 (3)	Exercise: 21.00±2.81 Control: 23.04±1.79	Exercise (8 people): 54.75±9.32 Control (8 people): 60.75±9.91	Homocysteine	Hemodialysis patients	16 females and males (11 females and 5 males)	RCT-Iran	Karimi et al. 2017 [14]
Running training at an intensity of 50% to 70% of maximum oxygen consumption	20 to 38	10 (3)	Exercise: 23.16±4.17 Control: 22.16±2.28	Exercise (13 people): 21.41±2.15 Control (13 people): 20.66±1.82	Homocysteine	Sedentary and obese	26 males	RCT-Iran	Aghamohammadi et al. 2015 [31]
Running or walking on a treadmill at 90% to 95% of maximum oxygen consumption	10 to 45	8 (3)	Exercise: 26.10±6.50 Control: 26.50±5.00	HIIT Exercise (10 people): 27.20±5.50 Control (10 people): 27.20±5.50	Homocysteine TC TG HDL LDL	Polycystic ovary syndrome	20 females	RCT – Norway	Almenning et al. 2015 [32]
Running training at an intensity of 60% to 75% of maximum oxygen consumption	60	8 (3)	Exercise: 25.59±1.95 Control: 26.60±1.95	Exercise (15 people): 41.46±3.10 Control (15 people): 41.06±4.00	Homocysteine	Type 2 diabetes	30 females	RCT – Iran	Hejazi et al. 2013 [33]
Bruce test exercise: running on a treadmill at an intensity of 60% to 75% of maximum heart rate	20 to 35	8 (3)	Exercise: 23.14±3.87 Control: 22.43±3.45	Exercise (14 people): 19.07±0.92 Control (14 people): 19.21±1.53	Homocysteine	Non-athlete	28 males	RCT – Iran	Bahram et al. 2013 [34]
Continuous running training at an	45 to 60	3 months (3)	Exercise: 27.43±2.78 Control:	Exercise (11 people): 44.73±4.43	Homocysteine TC TG	Healthy and inactive	21 males	RCT – Iran	Bizheh et al. 2012 [35]

Exercise intensity (%)	Workout duration (min)	Length of intervention in weeks (Number of sessions per week)	Body mass index (kg/m)	Age (Year)	Variables	Characteristics of the subjects	Sample (Gender)	Study Type-Country	Ref.
intensity of 75% to 85% of maximum heart rate			27.58±3.22	Control (10 people): 41.16±8.03					
Treadmill running exercise at an intensity of 60% to 70% of maximum oxygen consumption	20 to 40	6 (2)	Practice: - Control: -	Exercise (9 people): 00.68±00.7 Control (9 people): 00.68±00.8	Homocysteine	Parkinson's disease	18 females and males (8 females and 10 males)	RCT – New York	Donoghue et al. 2012 [36]
Treadmill running or intensity training at 60% to 75% of maximum heart rate	30 to 45	12 (3)	Exercise: 34.94±1.49 Control: 35.59±2.47	Exercise (10 people): 20 to 30 years old Control (10 people): 20 to 30 years old	Homocysteine	Obese	20 females	RCT – Iran	Taghian et al. 2011 [37]
Treadmill running training at an intensity of 50% to 70% of heart rate reserve	20 to 60	16 (3)	Exercise: 26.29±4.16 Control: 31.25±4.39	Exercise (15 people): 60 to 75 years old Control (15 people): 60 to 75 years old	Homocysteine	Non-athlete	30 females	RCT – Iran	Taghian and Esfarjani 2011 [38]
Rhythmic and step exercises at an intensity of 65% to 75% of maximum heart rate	60	8 (4)	Exercise: 32.63±3.55 Control: 30.58±2.32	Exercise (12 people): 21.81±2.40 Control (12 people): 21.50±2.56	Homocysteine	Obese	24 females	RCT – Iran	Azarniveh et al. 2011 [39]
Walking exercise on a treadmill at an intensity of 70% to 80% of maximum heart rate	30	8 (3)	Exercise: 22.00±1.99 Control: 21.50±1.42	Training (18 people): 21.50±2.28 Control (13 people): 21.75±2.67	Homocysteine TC TG HDL LDL	Inactive	31 females and males (18 females and 13 males)	NRC – Turkey	Sabasi et al. 2009 [40]
Aerobic exercise in a standing position, increasing intensity at 40% to 65% of maximum heart rate	15 to 40	8 (3)	Exercise: 25.56±4.94 Control: 26.43±3.85	Exercise (14 people): 67.38±3.37 Control (10 people): 67.30±4.73	Homocysteine	Non-athlete	24 females	RCT – Iran	Dehghan et al. 2009 [41]
Walking exercise on a treadmill at an intensity of 70% to 80% of maximum heart rate	30	8 (3)	Exercise: 22.00±1.99 Control: 21.50±1.42	Exercise (22 people): 21.50±2.28 Control (18 people): 21.75±2.66	Homocysteine TC TG HDL LDL	Healthy	40 females and males (23 females and 17 males)	RCT- Turkey	Gelecek et al. 2006 [42]

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Characteristics of Subjects

A total of 511 subjects were included in the present meta-analysis, all of whom were adults. In addition, 261 subjects were in the aerobic exercise group with a mean age of 42.45±4.23 years and a mean BMI of 26.77±4.27 years, while 250 subjects were in the control group with a mean age of 43.08±5.99 years and a mean BMI of 27.26±3.64 years. All participants were inactive before the start of the exercise protocol, and in all studies, the control group did not engage in any physical activity. The number of subjects in the studies ranged from a minimum of 16 [14] to a maximum of 45 [45].

Features of the Exercise Protocol

A total of 19 studies were included in the present meta-analysis, with a minimum of 20 min [13] and a maximum of 75 min [29] for each session of aerobic exercise. The exercise intensity for aerobic exercise was at least 40–70% [14] and at most 70–100% of maximal oxygen uptake [28].

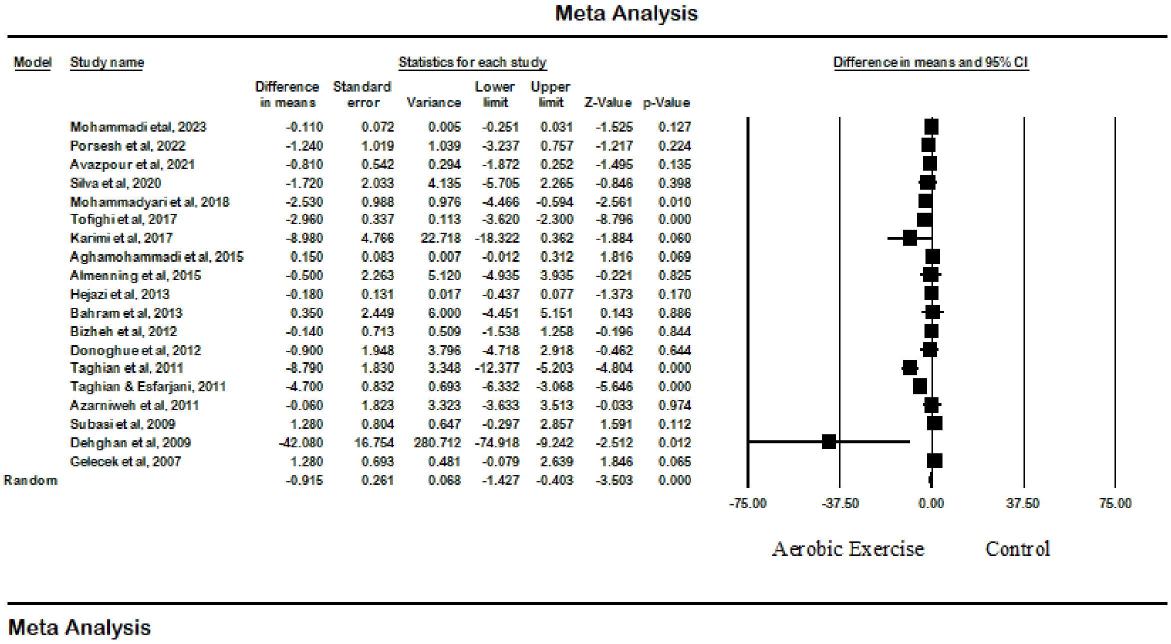
Meta-analysis Results

Homocysteine

The analysis of data from 19 interventions indicated that aerobic exercise significantly reduced homocysteine [WMD= -0.915, 95% CI: -1.427 to -0.403, P= 0.001] compared to the control group in adults (Figure 2). Heterogeneity was examined using the (I^2) test, and the results indicated that there was high and significant heterogeneity (P=0.001, I^2=88.841).

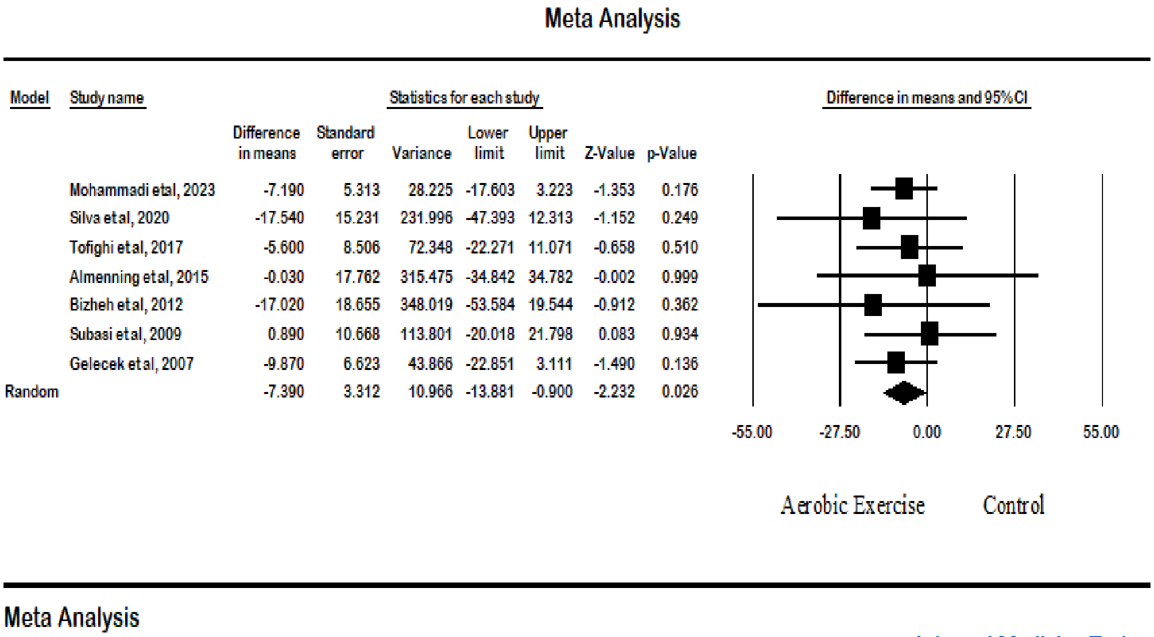
TC

Analysis of the data from the seven interventions showed that aerobic exercise significantly reduced TC [WMD= -7.390 mg/dL, 95% CI: -13.881 to -0.900, P= 0.026] compared to the control group in adults (Figure 3). Heterogeneity was assessed using the (I^2) test, and the results showed no significant heterogeneity (P=0.947, I^2=0.000).



Model	Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
	Mohammadi etal, 2023	-0.110	0.072	0.005	-0.251	0.031	-1.525	0.127
	Porsesh et al, 2022	-1.240	1.019	1.039	-3.237	0.757	-1.217	0.224
	Avazpour et al, 2021	-0.810	0.542	0.294	-1.872	0.252	-1.495	0.135
	Silva et al, 2020	-1.720	2.033	4.135	-5.705	2.265	-0.846	0.398
	Mohammadyari et al, 2018	-2.530	0.988	0.976	-4.466	-0.594	-2.561	0.010
	Tofighi et al, 2017	-2.960	0.337	0.113	-3.620	-2.300	-8.796	0.000
	Karimi et al, 2017	-8.980	4.766	22.718	-18.322	0.362	-1.884	0.060
	Aghamohammadi et al, 2015	0.150	0.083	0.007	-0.012	0.312	1.816	0.069
	Almenning et al, 2015	-0.500	2.263	5.120	-4.935	3.935	-0.221	0.825
	Hejazi et al, 2013	-0.180	0.131	0.017	-0.437	0.077	-1.373	0.170
	Bahram et al, 2013	0.350	2.449	6.000	-4.451	5.151	0.143	0.886
	Bizheh et al, 2012	-0.140	0.713	0.509	-1.538	1.258	-0.196	0.844
	Donoghue et al, 2012	-0.900	1.948	3.796	-4.718	2.918	-0.462	0.644
	Taghian et al, 2011	-8.790	1.830	3.348	-12.377	-5.203	-4.804	0.000
	Taghian & Esfarjani, 2011	-4.700	0.832	0.693	-6.332	-3.068	-5.646	0.000
	Azarniweh et al, 2011	-0.060	1.823	3.323	-3.633	3.513	-0.033	0.974
	Subasi et al, 2009	1.280	0.804	0.647	-0.297	2.857	1.591	0.112
	Dehghan et al, 2009	-42.080	16.754	280.712	-74.918	-9.242	-2.512	0.012
	Gelecek et al, 2007	1.280	0.693	0.481	-0.079	2.639	1.846	0.065
Random		-0.915	0.261	0.068	-1.427	-0.403	-3.503	0.000

Figure 2. Forest plot of the effect of aerobic exercise on homocysteine levels in adults.



Model	Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
	Mohammadi etal, 2023	-7.190	5.313	28.225	-17.603	3.223	-1.353	0.176
	Silva etal, 2020	-17.540	15.231	231.996	-47.393	12.313	-1.152	0.249
	Tofighi etal, 2017	-5.600	8.506	72.348	-22.271	11.071	-0.658	0.510
	Almenning etal, 2015	-0.030	17.762	315.475	-34.842	34.782	-0.002	0.999
	Bizheh etal, 2012	-17.020	18.655	348.019	-53.584	19.544	-0.912	0.362
	Subasi etal, 2009	0.890	10.668	113.801	-20.018	21.798	0.083	0.934
	Gelecek etal, 2007	-9.870	6.623	43.866	-22.851	3.111	-1.490	0.136
Random		-7.390	3.312	10.966	-13.881	-0.900	-2.232	0.026

Figure 3. Forest plot of the effect of aerobic exercise on TC levels in adults.

TG

Analysis of the data from the seven interventions showed that aerobic exercise did not significantly change TG [WMD= -3.418 mg/dL, 95% CI: -9.466 to 2.611, P= 0.266] compared to the control group in adults (Figure 4). Heterogeneity was examined using the (I^2) test, and the results indicated no significant heterogeneity (P=0.909, I^2=0.000).

HDL

Analysis of the data from the seven interventions showed that aerobic exercise did not significantly change HDL [WMD= 1.940 mg/dL, 95% CI: -0.920 to 4.799, P= 0.148] compared to the control group in adults (Figure 5). Heterogeneity was assessed using the I^2 test, and the results indicated no significant heterogeneity (P=0.300, I^2=17.044).

LDL

Data analysis of the seven interventions showed that aerobic exercise significantly reduced LDL [WMD= -8.934 mg/dL, 95% CI: -13.555 to -4.314, P= 0.001] compared to the control group in adults (Figure 6). Heterogeneity was assessed using the I^2 test, and the results showed no significant heterogeneity (P = 0.493, I^2=0.000).

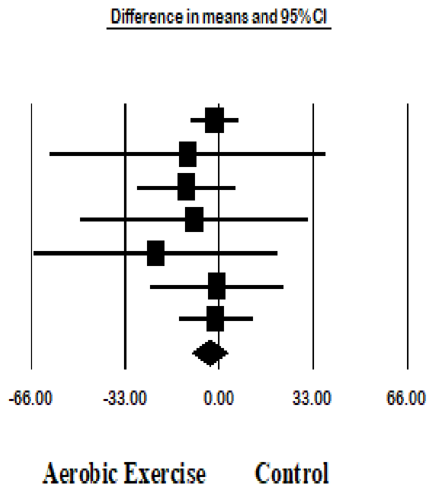
Table 2. Assessment of the quality of studies.

Study-year	1	2	3	4	5	6	7	8	9	Score
Mohammadi et al. 2023 [26]	✓	✓	×	×	✓	✓	×	✓	✓	6
Porsesh et al. 2022 [27]	✓	✓	×	✓	✓	✓	×	✓	✓	7
Avazpour et al. 2021 [28]	✓	✓	×	✓	✓	✓	×	✓	✓	7
Silva et al. 2020 [29]	✓	✓	×	×	✓	✓	×	✓	✓	6
Mohammadyari et al. 2018 [13]	✓	✓	×	✓	✓	✓	×	✓	✓	7
Tofighi el al. 2017 [30]	✓	✓	×	✓	✓	✓	×	✓	✓	7
Karimi et al. 2017 [14]	✓	✓	×	✓	✓	✓	×	✓	✓	7
Aghamohammadi et al. 2015 [31]	✓	✓	×	✓	✓	✓	×	✓	✓	7
Almenning et al. 2015 [32]	✓	✓	×	✓	✓	✓	×	✓	✓	7
Hejazi et al. 2013 [33]	✓	✓	×	✓	✓	✓	×	✓	✓	7
Bahram et al. 2013 [34]	✓	✓	×	✓	✓	✓	×	✓	✓	7
Bizheh et al. 2012 [35]	✓	✓	×	✓	✓	✓	×	✓	✓	7
Donoghue et al. 2012 [36]	✓	✓	×	✓	✓	✓	×	✓	✓	7
Taghian et al. 2011 [37]	✓	✓	×	✓	✓	✓	×	✓	✓	7
Taghian & Esfarjani, 2011 [38]	✓	✓	×	✓	✓	✓	×	✓	✓	7
Azarniveh et al. 2011 [39]	✓	✓	×	×	✓	✓	×	✓	✓	6
Sabasi et al. 2009 [40]	✓	✓	×	✓	✓	✓	×	✓	✓	7
Dehghan et al. 2009 [41]	✓	✓	×	×	✓	✓	×	✓	✓	6
Gelecek et al. 2006 [42]	✓	✓	×	×	✓	✓	×	✓	✓	6

Internal Medicine Today

Meta Analysis

Model	Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
	Mohammadi et al, 2023	-1.600	4.185	17.511	-9.802	6.602	-0.382	0.702
	Silva et al, 2020	-10.980	24.805	615.303	-59.598	37.638	-0.443	0.658
	Tofighi et al, 2017	-11.600	8.821	77.813	-28.889	5.689	-1.315	0.189
	Almenning et al, 2015	-8.860	20.390	415.764	-48.824	31.104	-0.435	0.664
	Bizheh et al, 2012	-22.300	21.860	477.867	-65.145	20.545	-1.020	0.308
	Subasi et al, 2009	-0.800	11.946	142.695	-24.213	22.613	-0.067	0.947
	Gelecek et al, 2007	-1.300	6.650	44.219	-14.333	11.733	-0.195	0.845
Random		-3.418	3.076	9.460	-9.446	2.611	-1.111	0.266



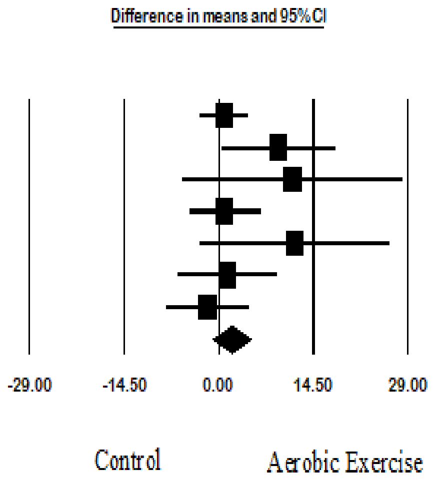
Meta Analysis

Internal Medicine Today

Figure 4. Forest plot of the effect of aerobic exercise on TG levels in adults

Meta Analysis

Model	Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
	Mohammadi et al, 2023	0.800	1.871	3.499	-2.866	4.466	0.428	0.669
	Silva et al, 2020	9.110	4.440	19.711	0.408	17.812	2.052	0.040
	Mohammadyari et al, 2018	11.230	8.670	75.161	-5.762	28.222	1.295	0.195
	Tofighi et al, 2017	0.900	2.826	7.984	-4.638	6.438	0.319	0.750
	Almenning et al, 2015	11.600	7.435	55.283	-2.973	26.173	1.560	0.119
	Subasi et al, 2009	1.300	3.858	14.885	-6.262	8.862	0.337	0.736
	Gelecek et al, 2007	-1.750	3.224	10.392	-8.068	4.568	-0.543	0.587
Random		1.940	1.459	2.129	-0.920	4.799	1.329	0.184



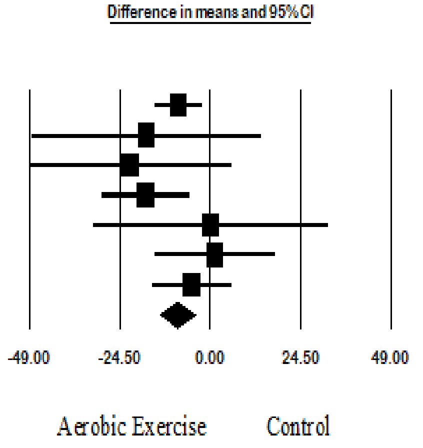
Meta Analysis

Internal Medicine Today

Figure 5. Forest plot of the effect of aerobic exercise on HDL levels in adults

Meta Analysis

Model	Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
	Mohammadi et al, 2023	-8.700	3.283	10.779	-15.135	-2.265	-2.650	0.008
	Silva et al, 2020	-17.350	15.843	251.002	-48.402	13.702	-1.095	0.273
	Mohammadyari et al, 2018	-21.650	13.907	193.391	-48.906	5.606	-1.557	0.120
	Tofighi et al, 2017	-17.500	6.084	37.018	-29.425	-5.575	-2.876	0.004
	Almenning et al, 2015	-0.010	16.175	261.639	-31.713	31.693	-0.001	1.000
	Subasi et al, 2009	1.190	8.268	68.365	-15.016	17.396	0.144	0.886
	Gelecek et al, 2007	-5.040	5.543	30.723	-15.904	5.824	-0.909	0.363
Random		-8.934	2.357	5.557	-13.555	-4.314	-3.790	0.000



Meta Analysis

Figure 6. Forest plot of the effect of aerobic exercise on LDL levels in adults

Publication Bias

The results of Egger's test indicated no significant publication bias for homocysteine (P= 0.363) and HDL (P= 0.060), as well as non-significant results for TC (P = 0.860) and LDL (P= 0.836).

Quality of Studies

The results of the quality assessment of articles using Pedro demonstrated that the minimum and maximum quality scores were 6 and 7, respectively.

Discussion

The present meta-analysis aimed to investigate the effect of aerobic exercise on homocysteine and lipid profiles in adults. The results of 19 studies with 511 subjects indicated that aerobic exercise significantly reduced homocysteine, TC, and LDL compared to the control group in adults. On the other hand, aerobic exercise did not change substantially TG and HDL compared to the control group.

Previous studies have also reported similar results; for example, Mohammadyari et al. (2018) showed that eight weeks of low-volume, high-intensity interval training reduced plasma homocysteine levels in overweight men [13]. In addition, Karimi et al. (2017) reported a significant reduction in homocysteine in hemodialysis patients after eight weeks of aerobic training [14]. However, another study observed a non-significant decrease in homocysteine in inactive overweight middle-aged women [27]. Bahram et al. [34] reported a non-significant reduction in homocysteine in non-athletic men [34]. These differences may be due to insufficient training volume in terms of intensity or duration, differences in fitness level, and a lack of complete control of participants' nutrition.

Possible mechanisms of homocysteine reduction after aerobic exercise include reduction of oxidative stress through increased homocysteine methylation, increased S-adenosyl methionine, and increased antioxidant capacity. In general, regular exercise training increases the metabolic requirement for methionine, which leads to a decrease in homocysteine, an intermediate in methionine metabolism [15].

Aerobic exercise can affect homocysteine levels and lipid profiles through various biological pathways. One of the essential mechanisms for reducing homocysteine after exercise is to improve the function of enzymes such as methionine synthase and increase the consumption of cofactors of vitamins B6, B12, and folate, which are involved in homocysteine metabolism and are increased by regular exercise [15]. Additionally, chronic aerobic exercise activates the AMPK pathway, leading to an increase in β-oxidation of fatty acids in mitochondria, which in turn reduces blood lipids, including triglycerides and LDL [46]. Aerobic exercise also improves the antioxidant/peroxidase ratio and inhibits the degradation of compounds, such as homocysteine, by reducing oxidative stress. On the other hand, the increase in lipoprotein lipase in skeletal muscle and adipose tissue after exercise leads to increased triglyceride uptake and increased HDL [47]. These biochemical pathways are key mechanisms in the role of aerobic exercise as a non-pharmacological strategy for improving cardiometabolic health in adults.

In the field of lipid profile, Mohammadyari et al. (2018) reported that eight weeks of high-intensity low-volume interval training reduced LDL and increased HDL [18]. Additionally, Tofighi et al. (2017) demonstrated a significant decrease in TG, TC, and LDL, along with a substantial increase in HDL, in obese women after eight weeks of aerobic training [30]. Elming et al. (2015) also reported a decrease in TG, TC, and LDL, and an increase in HDL, in women with polycystic ovary syndrome after ten weeks of aerobic training [32]. However, Sabasi et al. (2009) reported that they did not observe a significant change in these variables in sedentary individuals after eight weeks of training [40]. Gelecek et al. (2006) reported a significant decrease in TC and LDL, and a substantial increase in HDL, in healthy individuals [42]. These differences are likely due to variations in training protocols and the physiological and pathological conditions of the participants. The mechanisms of TC, TG, and LDL reduction, and HDL increase due to aerobic exercise include increased epinephrine secretion during exercise, which, via cyclic adenosine monophosphate, increases the release of free fatty acids from adipose tissue. This process occurs through the activation of lipases [48]. Physical activity appears to increase the skeletal muscle's capacity to utilize fat instead of glycogen, leading to a decrease in blood lipid levels [49]. The enzymes involved include increased activity of lecithin cholesterol acyltransferase (LCAT), which is responsible for the transfer of esters to HDL cholesterol, and lipoprotein lipase, as well as decreased activity of cholesterol ester transfer protein (CETP), which regulates the transfer of cholesterol from HDL to other lipoproteins. These enzymatic changes, together with improved fatty acid oxidation capacity, reduce VLDL cholesterol and TG [50].

The present study has several strengths. Given that differences in exercise type, duration, or intensity can affect the overall results of the meta-analysis, the exercise protocols of the included studies in this meta-analysis varied, encompassing different aerobic exercises. The limitations of the present study include the small sample size. From the available study data, it is clear that allocation concealment was not adequately reported in all randomized trials, which may introduce selection bias into this assessment. Additionally, none of the randomized controlled trials included in this analysis reported blinding of outcome assessors, which presents the possibility of potential selection bias in this assessment of the study. Therefore, further studies with larger sample sizes are necessary to confirm and strengthen the findings of the present study.

The results of this meta-analysis indicated that aerobic exercise can significantly reduce plasma homocysteine, total cholesterol, and serum LDL levels in adults. However, no significant effect was observed on HDL and TG levels. These findings suggest that aerobic exercise can be used as an effective and recommended non-pharmacological intervention for improving specific metabolic markers associated with cardiovascular diseases and type 2 diabetes.

However, given the heterogeneity in the type, intensity, and duration of exercise in the included studies, it is still not possible to propose a precise and general prescription for aerobic exercise that maximizes its effectiveness on lipid profiles and homocysteine levels. Therefore, future studies with more accurate designs, focusing on comparing different types of exercise protocols (in terms of intensity, duration, and kind of exercise), are necessary to determine the most effective exercise approach for the prevention and control of metabolic and cardiovascular diseases.

The present meta-analysis has significant strengths. One of the most important of these strengths is the use of data from 19 studies involving a total of 511 adult participants, which provided an adequate sample size for analyzing the effects of aerobic exercise on homocysteine and lipid profiles. Additionally, the included studies encompassed a wide range of aerobic exercise intensities and durations, thereby increasing the generalizability of the results to various types of aerobic exercise. A detailed analysis of the results, including effect size (SMD/WMD), significance level (P-value), and confidence interval range, increased the transparency and accuracy of reporting the findings. In addition, the examination of heterogeneity (I^2) and the absence of publication bias, as determined by the Egger test, further enhanced the validity of the results. Moreover, the quality of the included studies was generally assessed as moderate to good.

However, this meta-analysis also has limitations that should be taken into consideration. The significant heterogeneity observed in the homocysteine variable indicates substantial differences between studies in terms of exercise protocols, demographic characteristics, and participant physiological conditions, which could affect the accuracy of the results. Additionally, the sample size of some included studies was relatively small, which may limit the statistical power of specific analyses. The lack of complete information in some studies on dietary control, physical fitness level, and other contributing factors is another limitation. Finally, the lack of accurate reporting of some methodological details, such as blinding of assessors or allocation concealment, could increase the possibility of bias.

Given these limitations, it is recommended that future studies be conducted with larger samples, a more systematic design, and more precise control of confounding variables to provide more definitive results and more accurate recommendations regarding the type, intensity, and duration of aerobic exercise to improve homocysteine and lipid profiles.

Ethical Considerations

Compliance with ethical guidelines

The authors declare no conflicts of interest.

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Authors' contributions

OZ: Data curation, Formal analysis, Methodology, Software, Writing original draft, Writing – review & editing. FK: Conceptualization, Data curation, Formal analysis, Methodology, Software, Writing original draft, Writing – review & editing.

Conflicts of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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