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REVIEW ARTICLE

The Effects of Exercise Training on Genes Associated with Cardiovascular Disorders in Obese and Overweight People: A Systematic Review and Meta-Analysis

[1]Diako Heidary*, [2]Mostafa Bahremand, [3]Joseph Esformes

[1]Faculty of Physical Education and Sport Sciences, Allameh Tabataba'i University, Tehran, Iran. [2]Interventional Cardiologist, Associate Professor of Kermanshah University of Medical Sciences, Kermanshah, Iran. [3]Cardiff School of Sport and Health Sciences, Cardiff Metropolitan University, Cardiff, United Kingdom.

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ABSTRACT

Background. Abdominal obesity is a risk factor for cardiovascular disease (CVD) worldwide. **Objectives.** The present study aims to conduct a systematic review and meta-analysis of the effects of exercise training on genes associated with cardiovascular disorders in obese and overweight people. **Methods.** A database search (PubMed, Scopus, Web of Science, and Google Scholar) was conducted to identify controlled clinical trials in English. The search was conducted from March 01, 2024, until April 01, 2024. The relevant search terms were divided into three search levels. On the first search level, "Aerobic Exercise or Aerobic Training or Exercise Training or Resistance Exercise or Resistance Training or Physical Activity," on the second step, "AND (COL3A1 or FBN1 or TGFBR1 or TGFBR2 or SMAD3 or ACTA2 or MYH11 or MYBPC3 or MYH7 or TNNT2 or TNNI3 or TPM1 or MYL3 or ACTC1 or PRKAG2 or GLA or MYL2 or LMNA or RYR2 or PKP2 or DSP or DSC2 or TMEM43 or DSG2 or KCNQ1 or KCNH2 or SCN5A or LDLR or APOB or PCSK9)" and on the third step "AND (Obesity or Overweight or Obese)" were used as search terms. The mean difference (MD) with 95% confidence intervals (CIs) and the overall effect size was calculated for all comparisons. The PEDro scale was used to evaluate the quality of articles. **Results.** Our findings showed a significant effect of exercise training on ApoB (difference in means=0.035, Z=2.607, P=0.009), ApoA1 (difference in means=-0.018, Z=-2.176, P=0.030), and ApoB/ApoA1 ratio (difference in means=0.063, Z=5.026, P=0.000) in obese and overweight people. **Conclusion.** Exercise training intervention significantly increased ApoA1 and decreased ApoB. Therefore, obese and overweight people can improve the expression of genes related to cardiovascular disorders by participating in exercise programs.

KEYWORDS: ***Exercise Training, Cardiovascular Disorders, Gene Expression, Overweight, Obesity.***

INTRODUCTION

The "2013 AHA [American Heart Association]/ACC [American College of Cardiology]/TOS [The Obesity Society] Guideline for the Management of Overweight and Obesity in Adults" (1) uses the World Health Organization criteria (2) to define overweight as a body mass index (BMI) ≥25 and <30 kg/m^2 and obesity as a BMI ≥30 kg/m^2 (3). The GBD (Global Burden of Disease) Obesity Collaborators estimated that a total of 603.7 million adults had obesity, with obesity prevalence doubling between 1980 and 2015 in

*. Corresponding Author:
Diako Heidary, M.Sc.
E-mail: diako.heydari@gmail.com

73 countries and continuously increasing in most of the other countries (4). It is estimated that 39% to 49% of the world's population (2.8–3.5 billion people) have overweight or obesity (5). In addition, the GBD investigators found an increase in the burden of elevated BMI, with high BMI accounting for 4.0 million deaths in 2015, more than two-thirds of which were caused by cardiovascular disease (CVD), even after accounting for smoking and ill health (6, 7).

Cardiovascular disease mortality and morbidity are elevated in individuals who are overweight, particularly with central deposition of adipose tissues (8). Abdominal obesity is a risk factor for CVD worldwide (9). Obesity may be associated with hypertension, dyslipidemia, diabetes, insulin resistance, and elevated levels of fibrinogen and C-reactive protein, all of which increase the risk of CVD events (10). In addition to CVD, obesity has been shown to increase the risk of high blood pressure (HBP). Persistent hypertension is one of the risk factors for stroke, myocardial infarction (MI), heart failure, and arterial aneurysm. It is a leading cause of chronic kidney failure. Moderate elevation of arterial blood pressure leads to shortened life expectancy, which also increases the risk of heart disease (11).

Advances in human genetics are improving the understanding of various cardiovascular diseases, including cardiomyopathies, arrhythmic disorders, vascular disorders, and lipid disorders such as familial hypercholesterolemia. However, not all cardiovascular practitioners are fully aware of the utility and potential pitfalls of incorporating genetic test results into the care of patients and their families (12). The American College of Medical Genetics and Genomics (ACMG) has published a list of 59 medically actionable genes (known as the ACMG 59) recommended for return in clinical genetic testing that involves exome or genome sequencing (13). Notably, 30 ACMG 59 genes are related to cardiovascular diseases (12).

Over the past few decades, the effects of exercise and weight loss on lipoproteins and dyslipidemia have been elucidated (14). Also, the relationship between exercise and the reduction of cardiovascular diseases has been investigated, and it has been shown that exercise can reduce cardiovascular disorders through various mechanisms (15). However, few studies have been conducted on the effect of exercise on genes related to cardiovascular disorders. However, in previous studies, the positive effects of exercise on genes related to cardiovascular disorders have been reported (12).

It is well-established that exercise is beneficial for obese and overweight people (16). Still, our main question in the current study is whether exercise can help obese and overweight people by influencing genes related to cardiovascular disorders and reducing cardiovascular diseases in them. Therefore, the present study aims to conduct a systematic review and meta-analysis of the effects of exercise training on genes associated with cardiovascular disorders in obese and overweight people.

MATERIALS AND METHODS

Protocol and registration. The present systematic review study protocol was registered prospectively in the PROSPERO database with the registration code CRD42024525676.

Literature search strategy. The PRISMA strategies were applied to report this meta-analytical review (17). PubMed, Web of Science, Scopus, and Google Scholar databases were used independently by two researchers to extract eligible health and sport-related studies. The search was conducted from March 01, 2024, until April 01, 2024. The search conditions were divided into three steps and combined with Boolean sentences (AND/OR). On the first search step, "Aerobic Exercise or Aerobic Training or Exercise Training or Resistance Exercise or Resistance Training or Physical Activity," on the second step, "AND (COL3A1 or FBN1 or TGFBR1 or TGFBR2 or SMAD3 or ACTA2 or MYH11 or MYBPC3 or MYH7 or TNNT2 or TNNI3 or TPM1 or MYL3 or ACTC1 or PRKAG2 or GLA or MYL2 or LMNA or RYR2 or PKP2 or DSP or DSC2 or TMEM43 or DSG2 or KCNQ1 or KCNH2 or SCN5A or LDLR or APOB or PCSK9)" and on the third step "AND (Obesity or Overweight or Obese)" was used as research phrases. The screening process includes the title, abstract, and full text. First, all articles found in the search were screened manually by the two researchers and discussed for competency. All chosen titles were then moved to reference management software (EndNote, Version 20). Both researchers screened the abstracts separately and then discussed them. Irrelevant studies were excluded, and the full texts were screened for the final inclusion/exclusion of the articles.

Study inclusion and exclusion criterion. The PICOS approach, population (P), intervention (I), comparators (C), primary outcome (O), and study design consider (S) as tools for defined inclusion and exclusion criteria. Only studies with a full text published in English and with an aim group of obese and overweight people (P) were included in the meta-analysis. The inclusion criterion was that the study had to be an intervention study (I) with ET (At least two weeks) as a controlled trial. Each article had to have at least one control group (C). Genes associated with cardiovascular disorders (O) had to be reported as pre-tests and post-tests (S) in the article. Exclusion criteria were the use of dietary supplements or changes in the diet as part of the intervention.

Study selection. Two reviewers separately screened titles and abstracts. The full text of eligible studies was read. Disagreements were resolved by discussion between the two authors.

Methodological quality assessment. The methodological quality of the eligible randomized controlled trials was rated using the PEDro scales. The PEDro score includes 11 criteria (concealed allocation, random allocation, blind subjects, baseline comparability, blind assessor, blind therapists, intention-to-treat-analysis, adequate follow-up, point estimates, and variability between group comparisons), which receives either a "yes" or "no" rating. Also, the maximum PEDro concession is 10 points (15).

Data extraction. The results of the genes associated with cardiovascular disorders were extracted and transferred to a separate Excel sheet containing all the information for the relevant calculations described in the statistical analysis section. Year, authors, number of participants, body mass index (BMI), participants' gender, age of participants, details about the intervention, and summary of study findings) were also extracted (Table 1).

Table 1. Specifications of the analyzed randomized controlled trials

Study	Total sample size/gender	Age (year) (Mean±SD)	Body mass index (kg/m^2) (Mean±SD)	Intervention	Results	PEDro score
Mads Rosenkilde et al., 2018 (18)	60/ Male	_	_	Endurance training/ 12 weeks/ 3 sessions per week	Exercise-induced decline in body weight reduces pro-atherogenic apoB-containing lipoproteins. In contrast, exercise compensated by energy intake increases the key component of reverse cholesterol transport, i.e., ApoA1-containing high-density lipoprotein (HDL-C).	6
Tarcisio Santana Gomes et al., 2017 (19)	39/ Both	55.5±8.3	31.2±4.4	Aerobic exercise/ 24 weeks/ 3 sessions per week	In this post-hoc study, aerobic training did not promote relevant changes in the bone metabolism markers investigated.	7
Angela S. Alberga et al., 2015 (20)	304/ Both	15.6±1.4	34.6±4.5	3 exercise groups (Aerobic, Resistance, Combined)/ 22 weeks/ 4 sessions per week	Combined aerobic and resistance training decreased abdominal subcutaneous fat in overweight and obese adolescents. Compared to aerobic training alone, combined training caused greater improvements in the ApoB/ApoA-1 ratio.	7
Antonio Paoli et al., 2013 (21)	58/ Male	61±3.3	29.8±0.9	3 exercise groups (high-intensity circuit, low-intensity circuit, traditional endurance)/ 12 weeks/ 3 sessions per week	Findings indicate that high-intensity circuit training improves blood pressure, lipoproteins, and triglycerides more effectively than endurance or lower-intensity circuit training.	6

Study	Total sample size/gender	Age (year) (Mean±SD)	Body mass index (kg/m^2) (Mean±SD)	Intervention	Results	PEDro score
Suleen S Ho et al., 2012 (22)	64/ Both	53±1.3	32.8±1.3	3 exercise groups (Aerobic, Resistance, Combined)/ 12 weeks/ 5 sessions per week	Combination exercise provided greater weight loss, fat loss, and cardio-respiratory fitness benefits than aerobic and resistance training modalities.	7
Nikolaos P. E. Kadoglou et al., 2012 (23)	52/ Both	61.3±2.1	32.7±4.0	Resistance exercise/ 12 weeks/ 3 sessions per week	Long-term resistance training ameliorated glycemic control, insulin sensitivity, and ApoB/ApoA-I ratio in individuals with type 2 diabetes mellitus (T2DM). However, no significant benefits were observed in other cardiovascular risk factors.	6
Latifa Beltaifa et al., 2011 (24)	37/ Female	35±9	34.9±4.6	walk-run transition speed (WRTS) training/ 48 weeks/ 3 sessions per week	The WRTS training promoted a greater reduction in body mass, improved metabolic and cardiovascular risk factors, and enhanced cardiovascular fitness.	6
O Ben Ounis et al., 2010 (25)	32/ Both	13.3±0.4	31.3±0.6	Running, jumping, and playing with a balloon intended to encourage physical activity in the subjects/ 8 weeks/ 4 sessions per week	The results of this study document that dramatic reductions in the prevalence of metabolic syndrome and its associated factors in obese children can be achieved in 8 weeks through exercise training targeted at Fat max.	5
Holme et al., 2007 (26)	188/ Male	41-50	28.9±3.6	Endurance training/ 48 weeks/ 3 sessions per week	Physical exercise reduced the atherogenic burden as experienced by the reduction in apoB or apoB/apoA-I levels, but not by low-density lipoprotein (LDL-C) in healthy middle-aged men.	7
Saima Alam et al., 2004 (27)	18/ Both	59.5±2.5	30.6±2.0	Combined exercise/ 24 weeks	This study demonstrates that in type 2 diabetes, a supervised exercise program reduces VLDL apoB pool size, which may be due to a decrease in VLDL apoB secretion rate.	5

_: No data.

Statistical analysis. Statistical analyses were conducted using Comprehensive Meta-Analysis Software Version 2.0. We performed a meta-analysis to specify the change in pre-test and post-test gene data by calculating the standardized mean difference (SMD) between the intervention and control groups, with a 95% confidence interval (CI). Comprehensive Meta-Analysis was also used to analyze the heterogeneity of studies and Begg and Egger's tests to determine publication bias.

RESULTS

Based on the search strategy, 2093 studies were identified. After screening the articles, 113 studies were found to be related, with 99 studies excluded after reviewing their abstracts and full text based on inclusion and exclusion criteria. Finally, 10 articles met the inclusion criteria and were included in the study (Table 1). All studies included in this study have a PEDro score of 5 or higher, with a 6.2 average score (Figure 1).

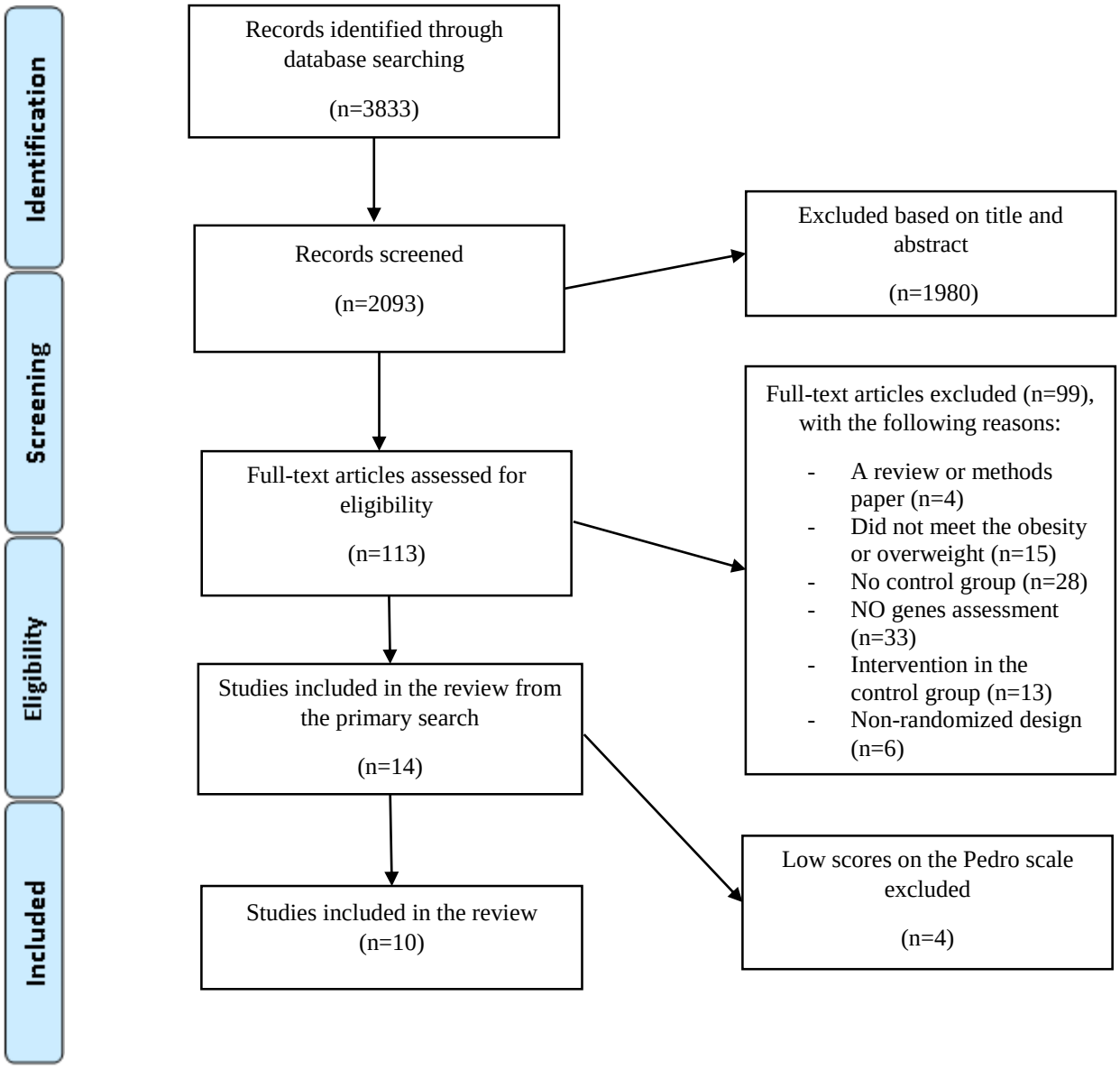


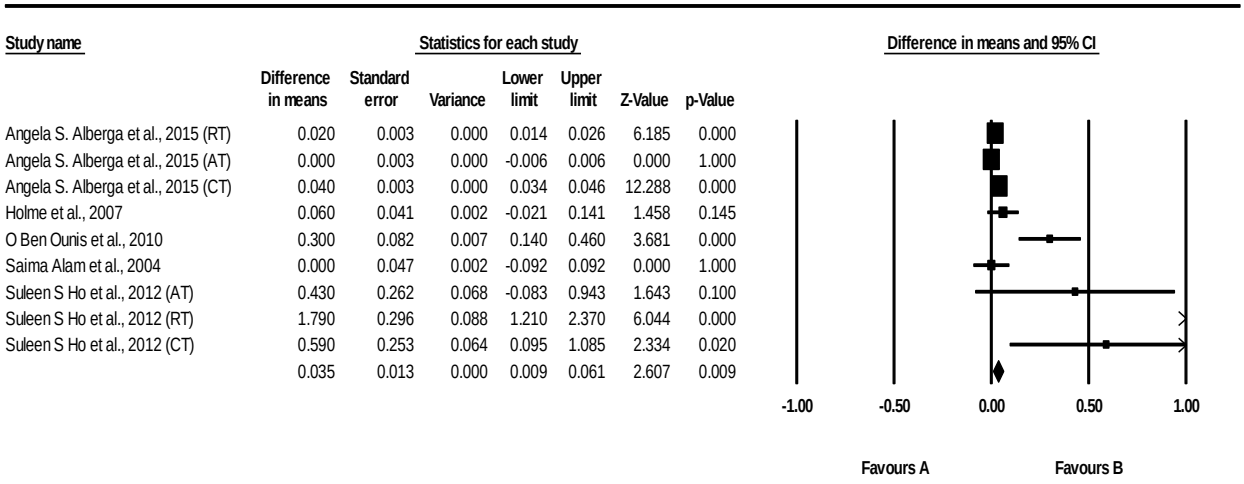
Figure 1. Flow diagram regarding article selection for the meta-analysis.

Based on our findings, various types of exercise can improve the status of genes associated with cardiovascular disorders in obese and overweight people (Table 1). However, several of these genes have not yet been studied in detail. ApoB and ApoA1 were the most frequently studied, allowing a meta-analysis to be conducted.

Our findings showed a significant effect of exercise training on ApoB in obese and overweight people (difference in means=0.035, Z=2.607, P=0.009; Figure 2). Therefore, our findings show that exercise training significantly decreases ApoB. No significant publication bias was identified based on Begg's test (P=0.12) and Egger's test (P=0.08). In other words, these findings are mainly trustworthy. An average value of 0.5 was used to determine the correlation between pre-test and post-test articles. The forest plots report the I2 statistic (total [95% CI]) due to the heterogeneity of the continuous data, with no significant heterogeneity observed (I2=64%, P=0.09).

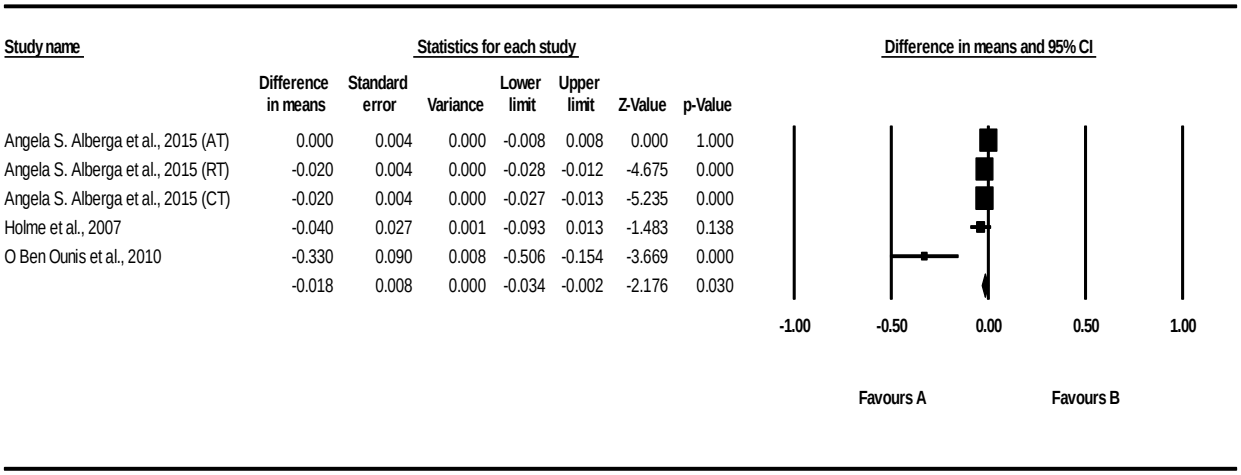
On the other hand, our findings showed a significant effect of exercise training on ApoA1 in obese and overweight people (difference in means=-0.018, Z=-2.176, P=0.030; Figure 3). Therefore, our findings show that exercise training significantly Increases ApoA1 in the intervention group. Based on the results of Begg's test (P=0.50) and Egger's test (P=0.15), this

research has no significant publication bias, making the findings essentially trustworthy. An average value of 0.5 was used to determine the correlation between pre-test and post-test articles. The forest plots report the I2 statistic (total [95% CI]) due to the heterogeneity of the continuous data, with no significant heterogeneity observed (I2=13%, P=0.28).



Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Angela S. Alberga et al., 2015 (RT)	0.020	0.003	0.000	0.014	0.026	6.185	0.000
Angela S. Alberga et al., 2015 (AT)	0.000	0.003	0.000	-0.006	0.006	0.000	1.000
Angela S. Alberga et al., 2015 (CT)	0.040	0.003	0.000	0.034	0.046	12.288	0.000
Holme et al., 2007	0.060	0.041	0.002	-0.021	0.141	1.458	0.145
O Ben Ounis et al., 2010	0.300	0.082	0.007	0.140	0.460	3.681	0.000
Saima Alam et al., 2004	0.000	0.047	0.002	-0.092	0.092	0.000	1.000
Suleen S Ho et al., 2012 (AT)	0.430	0.262	0.068	-0.083	0.943	1.643	0.100
Suleen S Ho et al., 2012 (RT)	1.790	0.296	0.088	1.210	2.370	6.044	0.000
Suleen S Ho et al., 2012 (CT)	0.590	0.253	0.064	0.095	1.085	2.334	0.020
	0.035	0.013	0.000	0.009	0.061	2.607	0.009

Figure 2. Meta-analysis of the effects of exercise training on ApoB in obese and overweight people, forest plot showings pooled mean differences with 95% cis for 9 effect sizes obtained from 5 trials. RT: Resistance Training; AT: Aerobic Training; CT: Combined Training.



Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Angela S. Alberga et al., 2015 (AT)	0.000	0.004	0.000	-0.008	0.008	0.000	1.000
Angela S. Alberga et al., 2015 (RT)	-0.020	0.004	0.000	-0.028	-0.012	-4.675	0.000
Angela S. Alberga et al., 2015 (CT)	-0.020	0.004	0.000	-0.027	-0.013	-5.235	0.000
Holme et al., 2007	-0.040	0.027	0.001	-0.093	0.013	-1.483	0.138
O Ben Ounis et al., 2010	-0.330	0.090	0.008	-0.506	-0.154	-3.669	0.000
	-0.018	0.008	0.000	-0.034	-0.002	-2.176	0.030

Figure 3. Meta-analysis of the effects of exercise training on ApoA1 in obese and overweight people, forest plot showings pooled mean differences with 95% cis for 5 effect sizes obtained from 3 trials. RT: Resistance Training; AT: Aerobic Training; CT: Combined Training.

A significant effect of exercise training on the ApoB/ApoA1 ratio was observed in obese and overweight people (difference in means=0.063, Z=5.026, P=0.000; Figure 4), showing that exercise training significantly decreases ApoB/ApoA1 in the intervention group, with no publication significant bias based on the results of Begg's test (P=0.45) and Egger's test (P=0.13). An average value of 0.5 was used to determine the correlation between pre-test and post-test articles. The forest plots report the I2 statistic (total [95% CI]) due to the heterogeneity of the continuous data, with no significant heterogeneity observed (I2=36%, P=0.21).

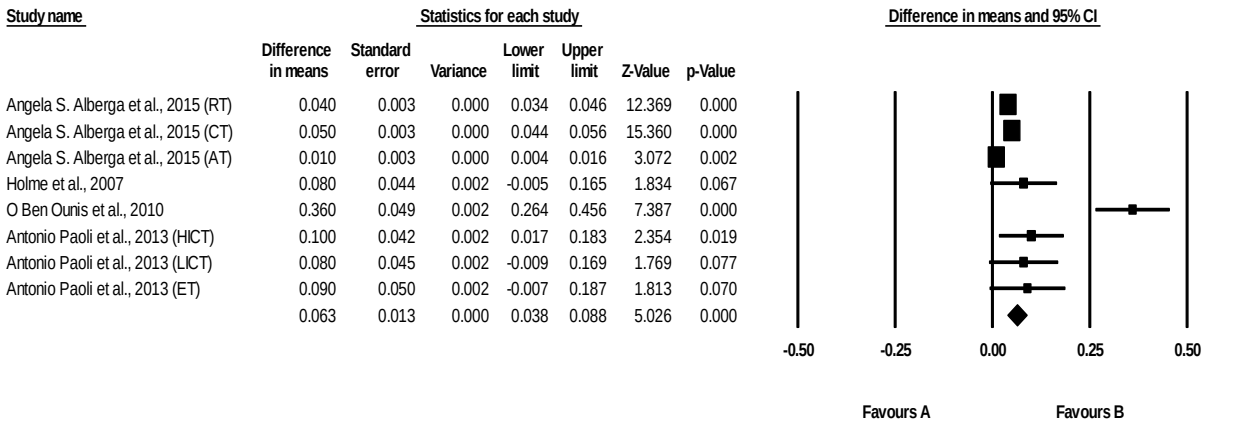


Figure 4. Meta-analysis of the effects of exercise training on ApoB/ApoA1 ratio in obese and overweight people, forest plot showings pooled mean differences with 95% cis for 8 effect sizes obtained from 4 trials. RT: Resistance Training; AT: Aerobic Training; CT: Combined Training; HICT: High-Intensity Circuit Training; LICT: Low-Intensity Circuit Training; ET: Endurance Training.

DISCUSSION

Based on our findings, exercise training can improve the expression of genes related to cardiovascular disorders in obese and overweight people, specifically by increasing ApoA1 and decreasing ApoB and ApoB/ApoA1. The ApoA1 gene provides instructions for making a protein called apolipoprotein A-I (ApoA-I). ApoA-I is a component of high-density lipoprotein (HDL) (28). Also, The APOB gene provides instructions for making two versions of the apolipoprotein B protein: a short version called apolipoprotein B-48 and a more extended version known as apolipoprotein B-100 (29). Because there is one ApoB per LDL particle, regardless of density, ApoB detects the presence of these atherogenic particles, in contrast to LDL cholesterol, and thus may be better suited to guide lipid-lowering therapy (30).

It is well-documented that total cholesterol, low-density cholesterol (LDL-C), apolipoprotein A-I (ApoA-I), and apolipoprotein B (ApoB) exert high-predictive value in major cardiovascular events in the general population (31). Notably, LDL-C levels are not always a good or adequate indicator of cardiovascular risk. The ApoB/ApoA-I ratio indicates better cardiovascular disease (CVD) risk than LDL-C (32).

In the current study, many studies show that exercise improves the lipid profile in obese and overweight people by improving the ratio of ApoB/ApoA1. After improving the lipid profile, many cardiovascular risks and disorders are improved (23, 25, 27). In some studies, the effects of different exercise training are compared, and they concluded that combined exercises cause more improvement in ApoB and ApoA-1 compared to aerobic exercises or resistance exercises alone (20, 22). Also, high-intensity circuit training improves blood pressure, lipoproteins, and triglycerides more effectively than endurance training alone or lower-intensity circuit training (21).

Of course, the effects of exercise are not limited to ApoB and ApoA1 genes, and regular exercise has been shown to improve the expression of genes related to cardiovascular disorders through various mechanisms (33). One fundamental way is by activating transcription factors that regulate gene expression. For example, exercise can activate the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) transcription factor, which is crucial in regulating mitochondrial biogenesis and oxidative metabolism in muscle cells (34). Exercise training has increased the expression of PGC-1α and its downstream target genes involved in mitochondrial function and antioxidant defense in human skeletal muscle (35). This upregulation of gene expression improves cardiovascular health by enhancing energy production, reducing

oxidative stress, and improving vascular function (36). Furthermore, exercise-induced changes in DNA methylation patterns can also modulate gene expression related to cardiovascular health (33).

Overall, exercise benefits gene expression related to cardiovascular disorders by activating transcription factors, modulating DNA methylation patterns, and other epigenetic mechanisms. These molecular changes contribute to the overall cardioprotective effects of regular physical activity (37).

Exercise has been shown to improve the expression of genes related to cardiovascular disorders in several ways:

1 .Exercise can increase the expression of genes involved in antioxidant defense mechanisms, which help protect against oxidative stress and inflammation that can contribute to cardiovascular disease (38).

2 .Exercise can improve the expression of genes involved in lipid metabolism, which can help regulate cholesterol levels and reduce the risk of atherosclerosis and heart disease (39).

3 .Exercise can enhance the expression of genes involved in vascular function, such as those that regulate blood pressure, blood vessel dilation, and blood flow, which can help improve overall cardiovascular health (40).

4 .Exercise can also influence gene expression related to insulin sensitivity and glucose metabolism, which can help prevent diabetes and other metabolic disorders that are risk factors for cardiovascular disease (41).

Regular exercise can positively impact gene expression patterns associated with cardiovascular health, reducing the risk of developing cardiovascular disorders. Since obese and overweight people are at risk of cardiovascular diseases, exercise training, especially combined exercise (aerobic and resistance), can help them a lot.

CONCLUSION

This review study shows that obese and overweight people can improve the expression of genes related to cardiovascular disorders by participating in exercise programs. Exercise training intervention significantly increased ApoA1 and decreased ApoB. However, more studies are needed on the effect of different types of exercise training on genes associated with cardiovascular disorders in obese and overweight people as well as other populations.

APPLICABLE REMARKS

- It is suggested that doctors prescribe exercise training for their obese patients and thereby prevent cardiovascular diseases in them.
- It is suggested that trainers should use more combined exercises for obese and overweight people and thus prevent cardiovascular disorders in them.

AUTHORS' CONTRIBUTIONS

Study concept and design: Diako Heidary. Acquisition of data: Diako Heidary, Mostafa Bahremand. Analysis and interpretation of data: Diako Heidary, Mostafa Bahremand. Drafting the manuscript: Diako Heidary. Critical revision of the manuscript for important intellectual content: Mostafa Bahremand, Joseph Esformes. Statistical analysis: Diako Heidary. Administrative, technical, and material support: Mostafa Bahremand. Study supervision: Joseph Esformes.

CONFLICT OF INTEREST

The authors mention no "Conflict of Interest" in this study.

ETHICAL CONSIDERATION

Not applicable.

FUNDING/SUPPORT

This study has no funding or support for the paper.

ROLE OF THE SPONSOR

The funding organizations are public institutions and had no role in the design and conduct of the study.

FINANCIAL DISCLOSURE

This study has no financial interests related to the material in the manuscript.

ARTIFICIAL INTELLIGENCE (AI) USE

This study agrees with the journal's policy in this section.

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