The Effect of Aerobic Exercise on Metabolic Parameters of Patients with Non-Alcoholic Fatty Liver Disease: Systematic Review and Meta-Analysis

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Abstract

Many studies have investigated the effect of aerobic exercise on factors associated with non-alcoholic fatty liver disease. Aerobic exercise is an essential component in the management and treatment of non-alcoholic fatty liver disease. The aim of this study was to determine and evaluate the effect of aerobic exercise on fasting blood glucose, Insulin, Insulin resistance, Glycosylated hemoglobin (Hemoglobin A1C), Lipid profile as important indicators of non-alcoholic fatty liver disease.

Methods: This research is a systematic review and meta-analysis that was conducted in 2021. For the present study, databases, ScienceDirect, PubMed, Scopus, science of Web, SID, Magiran and Google Scholar from 2010 to 2021, were searched along with keywords. After the initial screening, the full text of the articles was evaluated and the articles that met the inclusion criteria were analyzed. A total of 120 articles were reviewed, of which 16 articles met the criteria for entering the systematic review and meta-analysis. Accordingly, 710 people with fatty liver disease were divided into two groups of control and experimental group of 307 and 403 people, respectively. The mean age of the subjects in the present study was 52±10 years. The intervention effects were evaluated using the mean difference (MD) and the random effects model. Data were analyzed using effect size tests, bias analysis and heterogeneity analysis and by STATA software.

Results: Meta-analysis results indicated that endurance training in general significantly reduced glucose levels (P = 0.004, SDM = -0.26, SE = 0.09), insulin (P = 0.01, SDM = -0.29, SE = 0.11), HOMA-IR (P = 0.01, SDM = -0.28, SE = 0.11), Hba1c (P = 0.001, SDM = -0.33, SE = 0.12), triglycerides (P = 0.02, SDM = -0.31, SE = 0.13) and LDL (P = 0.03, SDM = -0.21, SE = 0.1). The results of meta-analysis did not show a significant effect on HDL levels after aerobic exercise in patients with fatty liver (P = 0.97, SDM = 0, SE = 0.09).

Conclusion: Endurance training improves the levels of glucose, insulin, Hba1c, Homa-IR, triglyceride, and LDL; although, there was no significant change in HDL levels due to endurance training. However, there is still a need for more and higher quality research in this area.

Introduction:

The prevalence of fatty liver disease in the world is about 20% of the world's population and is expected to reach 39.1% by 2035 [1]. More than 21.5% of Iran's population has fatty liver [2]. Fatty liver disease can be generally divided into non-alcoholic (NAFLD) and non-alcoholic steatohepatitis (NASH) [3]. Non-alcoholic fatty liver shows itself without inflammation, which is pathologically difficult to differentiate with NASH. One of the ways to differentiate them is to examine the body biopsy, which of course can be distinguished according to indicators such as steatosis, lobular inflammation and fibrosis [4]. In obese people, fatty liver disease occurs due to changes in dietary patterns. Among obesity-related diseases, non-alcoholic fatty liver disease (NAFLD) can be a risk factor in obese people and patients with type 2 diabetes due to its lack of specific symptoms and so-called silence. According to studies, increased blood glucose and insulin resistance, and consequently visceral and subcutaneous fat, which is usually associated with abdominal obesity in sedentary individuals, can lead to NAFLD [5]. The prevalence of non-alcoholic fatty liver disease in Western countries is about 35 – 32% and in Asia 19–32%. It's prevalence in obese people and patients with type 2 diabetes reaches 92 – 12%. However, because there is no specific symptom in this disease, many people do not know about the existence of this disease and there are no exact statistics about it [6]. Insulin resistance is one of the most important early pathophysiological mechanisms in the development of this disease, in which the amount of insulin secreted by the islets of the pancreas Langerhans decreases and can be associated with a decrease in insulin-sensitive receptors on the muscles. These factors can raise blood glucose and prevent the body's consuming tissues from absorbing blood sugar. Because the liver is more sensitive than other tissues to absorbing blood glucose, it begins to absorb glucose from the blood and convert it to glycogen. However, due to the limited capacity of the liver to store glycogen, the rest of the glucose absorbed by the liver is converted to fat and surrounds the liver, so insulin resistance is significantly associated with abnormal accumulation and excessive liver fat [5]. Because there is no specific drug for the definitive treatment of NAFLD, many physicians and specialists at the American Society for Internal and Metabolic Diseases recommend a sedentary lifestyle change and regular physical activity with dietary restrictions to manage and treat it to these patients [7]. Therefore, many scientific studies in the field of sports physiology and health have confirmed the significant effects of sports activities on the treatment and management of NAFLD disease through various training methods. These studies have demonstrated that regular physical activity can alter the metabolic parameters of these individuals and the fats that surround the liver [8]. In order to achieve this goal, each of these studies has adopted various training methods such as resistance and aerobic. Most of them have also achieved positive results and have shown that exercise can help reduce or even cure the destructive effects of fatty liver disease by altering homeostasis and forcing the body to metabolize more. Aerobic exercise has traditionally been the best training model studied in interventions related to patients with fatty liver. This exercise model, using large muscle groups, can improve many side effects associated with this disease, such as insulin resistance, hyperglycemia, and lipid profile in these patients [9]. However, the American College of Sports Medicine recommends that patients with fatty liver disease consume at least 1,000 kcal per week through physical activity [9]. Various studies have examined the effect of aerobic exercise on metabolic parameters of patients with NAFLD in human and animal samples and reported varied and even contradictory responses. Some results of meta-analysis studies have indicated that aerobic exercise can significantly improve the control of glycemic index in patients with fatty liver [10]. For example, in a study by Keating et al., A systematic review and meta-analysis found that aerobic exercise reduced insulin in these patients [11]. These researchers' meta-analysis results showed that exercise can reduce abdominal obesity and body mass index. Given that so far, no meta-analysis has been done regarding the effect of aerobic exercise on the metabolic parameters of NAFLD patients and it is certainly not possible to comment on it; as well as, the prevalence of NAFLD on the one hand and the scattering of studies in this field on the other hand, and the need to properly orient this research and provide a model to determine the best intensity of aerobic exercise for this disease, this study was conducted. This study was aimed to determine the effect of aerobic exercise on metabolic parameters of patients with non-alcoholic fatty liver disease, systematic review and meta-analysis.

Methods:

This research is a systematic review and meta-analysis study that was conducted in 2021 based on Cochrane's guidelines. Accordingly, to determine the intervention research, databases, Sid, ISI, Google Scholar, Embase, PubMed, Science Direct, Scopus and publications of the Ministry of Science were examined to find valid articles by combining the following textual words to formulate a search strategy in the target databases.

[exercise OR training OR physical activity OR insurance training] AND, NAFLD, NAFL, NASH, nonalcoholic steatohepatitis, non-alcoholic fatty liver disease, fatty liver, hepatic steatosis, and liver steatosis].

Based on searches in databases, 220 articles were selected and after the initial review of related articles, 120 articles entered the evaluation stage. After reviewing the full text of the remaining articles, if the articles met the inclusion criteria, their information was extracted. Therefore, a total of 20 articles were included in the meta-analysis (flowchart 1). Accordingly, 710 people with NAFLD were divided into control and experimental groups of 307 and 403 people, respectively. The mean age of the subjects in the present study was 52 ± 10 years.

Inclusion criteria of the present study articles included studies that had more than 4 weeks of practice intervention, including people with NAFLD, and articles that had merely human samples and were clinical trials. As well as, the studies in which aerobic exercise have been performed on people with NAFLD.

According to the exclusion criteria, studies with the following characteristics were excluded: review articles, case reports, animal studies, conference papers, articles with inappropriate data for statistical analysis, studies that examined resistance training, and duplicate studies.

The following information were extracted from the articles after the initial review: name of the first author of the article, year of publication, city of study, sample size, age, gender of participants, sampling method, sport program specifications, type of exercise, intensity and duration of training. The text quality of the articles was evaluated by two expert referees using the Cochrane checklist [12]. The results of research biases indicate asymmetry. Research bias can also affect the results of content analysis, such as the date of publication of anomalous data. The collected data were analyzed by STATA software and statistical tests to determine the effect of standardized mean difference.

Table 1 Specifications of studies performed on individuals with NAFLD entered in a systematic review and meta-analysis

Exercise intensity	Marker	BMI	age	Control group NO.	Experimental group NO.	Total NO.	sex	Disease	type	Author (year)
High intensity	Glucose Hba1c Insulin Triglyceride HOMA-IR	C: 32± 6 E: 31± 5	C: 59± 9 E: 61± 9	14	14	28	Male/female	NAFLD	Aerobics	Cassidy et al (2013) [13]
High intensity	Glucose Insulin HDL LDL Triglyceride HOMA-IR	C: 29.3± 3.7 E: 30.7± 4.3	C: 37.7± 6.6 E: 36.0± 6.9	15	23	38	Male/female	NAFLD	Aerobic, cycling	Chen et al (2008) [14]
Moderate, 60% HRR	Glucose HDL LDL Triglyceride HOMA-IR	29.7	50	31	38	69	Male/female	NAFLD	Aerobic and treadmill	Cuthbertson et al (2016) [15]
Moderate	Glucose Insulin	34.7 ± 6.4	50 ± 11	14	41	55	Male/female	NAFLD	Aerobics	Eckard et al (2013) [16]
NR	Glucose Insulin Hba1c HDL LDL Triglyceride HOMA-IR	26.9	67.4-76.3	50	50	100	Male/female	NAFLD	Aerobics	Finucane et al (2010) [17]
High intensity	Glucose Insulin Hba1c Triglyceride HOMA-IR	31	54	12	11	23	Male/female	NAFLD	Aerobics	Hallsworth et al (2015) [18]
moderate	Glucose Insulin Triglyceride	C: 35 ± 8 E: 33 ± 6	C: 45 ± 14 E: 50 ± 9	16	13	29	Male/female	NAFLD	Aerobics, compound exercises	Hickman et al (2013) [19]
NR	Glucose Insulin Hba1c Triglyceride HOMA-IR	C:33 E:33	C:51 E:54	12	12	24	Male/female	NAFLD	Aerobics, cycling	Houghton et al (2017) [20]

Exercise intensity	Marker	BMI	age	Control group NO.	Experimental group NO.	Total NO.	sex	Disease	type	Author (year)
Moderate	Glucose Insulin HDL LDL Triglyceride	31-36	39-45	12	48	60	Male/female	NAFLD	Aerobic	Keating et al (2015) [11]
NR	Glucose Insulin Hba1c HOMA-IR	C:33.7 E:33.9	C:47.6 E:47.9	34	33	67	Male/female	Adults with NASH	Aerobic	Promrat et al (2010) [21]
Moderate, 60% HRR	Glucose HDL LDL Triglyceride	C: 26-34 E: 29-33	C: 38-57 E: 44-56E: 39.7 ± 6.3	5	6	11	Male/female	Adults with NAFLD	Aerobics, 30-45min a day treadmill, 45 min per session	Pugh et al (2013) [22]
Moderate, 60% HRR	Glucose Insulin HDL LDL	C: 28-31 E: 30-32	C: 43-51 E: 44-51	20	34	54	Male/female	NAFLD	Aerobics, treadmill, Ergometer bike 30 to 45 min per session	Pugh et al (2014) [23]
NR	Glucose Insulin Hba1c HDL LDL Triglyceride	C:32.2 E:33.6	C:12.9 E:12.9	27	31	58	Male/female	NFALD	Aerobics	Savoye et al (2014) [24]
NR	Glucose Insulin HDL LDL Triglyceride	C: 32.9. ± 3.5 E: 32.4 ± 3.9	C: 55 ±6 E: 54± 4	21	22	43	Male/female	NFALD	Aerobics	Straznicky et al (2012) [25]
Low intensity, 45-55% VO2Peak	HDL LDL	C: 40.1 ± 2.1 E: 37.1 ± 1.1	NR	12	6	18	NR	Adults with NFALD	Aerobics, walking	Sulivan et al (2012) [26]
NR	Glucose Insulin HDL Triglyceride	C: 28.4±1 E: 27.3±1.1	C: 52±2 E: 61±2	18	15	33	NR	Adults with NASH	Aerobic, cycling, running, walking	Yoshimura et al (2014) [27]

Results:

The results of an analysis of 16 clinical trials performed on people associated with NAFLD indicated that endurance exercises improve the metabolic parameters of fatty liver. The results of meta-analysis suggested the significant reduction of glucose, insulin, HOMA-IR, Hba1c triglyceride, LDL levels by aerobic exercise. Fifteen studies were associated with glucose levels. According to Diagram 1, aerobic exercise reduced glucose levels (P = 0.004) and heterogeneity between studies was low (I2 = 18%). Thirteen studies were related to insulin levels and the heterogeneity between studies was moderate (I2 = 40%). As you can see in Diagram 2, endurance training significantly reduced insulin levels (P = 0.01, SDM = -0.29, SE = 0.11). Seven articles examined HOMA-IR levels and there was no heterogeneity between studies (I2 = 0%). As illustrated in Diagram 3, endurance training significantly reduced insulin resistance (P = 0.01, SDM = - 0.28, SE = 0.11). The number of studies related to HBA1C levels was 6 and there was no heterogeneity between them (I2 = 0%). According to Diagram 4, endurance training significantly reduced Hba1c levels (P = 0.001, SDM = -0.33, SE = 0.12). Twelve studies were related to triglyceride levels and the heterogeneity between them was moderate (I2 = 40%). As you can see in Diagram 5, endurance training significantly reduced triglyceride levels (P = 0.02, SDM = - 0.31, SE = 0.13). Ten studies were related to HDL levels with no heterogeneity between studies (I2 = 0%). As demonstrated in Diagram 6, endurance training significantly reduced HDL levels (P = 0.97, SDM = 0, SE = 0.09). Nine studies were related to LDL levels with no heterogeneity between them (I2 = 0%). According to Diagram 7, endurance training significantly reduced LDL levels (P = 0.03, SDM = -0.21, SE = 0.1).

Data extraction and Studies quality assessment: The following information were extracted from the articles after the initial review: name of the first author of the article, year of publication, city of study, sample size, age, gender of participants, sampling method, specifications of sports program. Quality of articles was assessed by two expert referees b the Cochrane checklist [28] (Figure 2). In the case of disagreement between them, it was controlled by the third referee. The Cochrane checklist examined issues related to research bias, such as the hierarchy of individuals in control and experimental groups, participants' lack of knowledge about study groups, and laboratory staff's lack of knowledge. Based on Cochrane evaluation, the degree of bias in four studies was low risk (23, 24) and was unclear in the other 16 studies. Sensitivity analysis was performed to affect the study and studies, and asymmetric evaluation was performed by symmetric regression test and Begg's test.

Statistical Analysis:

All variables in the experimental and control groups were analyzed using the standardized mean difference with a 95% confidence coefficient. Heterogeneity of studies was examined with the square I index. Due to the type of studies and the non-uniformity of the data, the Random Effect Model was used. Statistical analysis was performed by this STATA software. Significance level was also considered P <0.5.

Discussion:

This study was aimed to investigate the effect of aerobic exercise on metabolic indices of patients with ANFLD. The results of meta-analysis of 16 clinical trials indicated that aerobic exercise in NAFLD patients reduced levels of glucose, insulin, HOMA-IR, Hba1c triglyceride, LDL. Previous review studies have also studied the effect of exercise on NAFLD patients. Van et al. (2018) in their review study stated that exercise increases the oxidation of fatty acids and reduces damage to mitochondria and cited physical activity as an important strategy to treat this disease [29]. Hashida et al. (2017) in their review study with emphasis on strength training indicated the usefulness of strength training useful for these patients [30]. In their review, Takahashi et al. mentioned that physical activity is a powerful way to reduce the pathogenesis of NAFLD [31].

Factors that improve metabolic parameters by aerobic activity include reduced intrahepatic fat content, which aerobic exercise modulates intrahepatic fat content. Other factors include reduced oxidative stress and NAFLD-induced hepatitis [32]. Improved insulin function also appears to be a key factor in improving NAFD [33]. Improved insulin function is due to the effect of moderate to intense physical activity on total body fat, especially visceral fat [33]. Moreover, aerobic exercise increases the density of the capillary network in the liver, which is another factor affecting liver metabolic indices [34]. In line with the results of our research, studies by Cuthbertson et al. (2016), Savoye et al. (2013) [24] and Yoshimura et al. (2014) [27]on the effect of aerobic exercise on glucose levels in patients with NAFLD, indicated a decrease in the level of this index due to sport activities. In contrast, a study by Chen et al. (2008) [14] and Hickman et al. (2013) [19] found that aerobic exercise had no effect on lowering glucose levels. This difference was because of different types of exercises with different intensities. Regarding the metabolic index of Insulin, in line with our research in Cassidy et al. (2016) [13] and Keating et al. (2015) [11], aerobic exercise has been shown to reduce insulin levels. However, a 2013 study by Eckard et al. and Finucane et al. in 2010 found no significant reduction in the effect of aerobic exercise on insulin levels. These discrepancies seem to be apparent in different studies due to different baseline insulin levels. Also, the characteristics of the people involved in their study were different and some of them had diabetes. Hickman et al. (2013) [19] and Christopher et al. (2013) in their studies on Triglyceride found that aerobic exercise reduced Triglyceride levels. In contrast, in 2014 [28] Yoshimura et al. and in 2010 Finucane et al. did not report a decrease in Triglyceride levels. A study conducted by Straznicky et al. (2012) and Keating et al. (2015) [11] on the effect of aerobic exercise on LDL metabolic index and LDL reduction, and Sullivan in 2012 [26] stated the opposite in his research.

Regarding the HOMA-IR index, Cuthbertson reported in 2016 that aerobic exercise reduced this index, whereas Finucane et al. (2010) did not report a decrease. Regarding the effect of aerobic exercise on HDL levels, Keating and Cuthbertson et al. (2015) did not report a decrease in HDL levels after aerobic activity [15]. But Christopher et al. (2014 and 2013) reported aerobic exercise as effective in increasing HDL levels. These differences were seemingly due to the different baseline levels of metabolic indicators of the individuals involved in the interventions. Moreover, each of the studies used different types of aerobic exercises with different intensities to achieve this goal. Due to the variety of exercises and their intensity and duration, each has a unique effect on these patients. For example, some studies have shown that higher-intensity aerobic exercise has a greater effect on NAFLD metabolic index than moderate-intensity exercise [35]. However, in research, low- and moderate-intensity aerobic exercise is preferred to high-intensity endurance exercise, although the health benefits of high-intensity endurance exercise appear to be greater. This is because low-intensity exercise is less likely to cause medical accidents and people with fatty liver are able to do so.

The results of our HDL analysis demonstrated that aerobic exercise slightly increased it. Of course, the heterogeneity of studies in this field was high and for more definite conclusions, higher quality and more research is needed. In general, aerobic exercise seems to have traditionally been the best model for intervention in relation to this disease. It seems that aerobic exercise for large muscle groups can improve many side effects associated with this disease such as insulin resistance, hyperglycemia and lipid profile. Aerobic exercise can help decrease or even treat the destructive effects of fatty liver disease by altering homeostasis and forcing the body to metabolize [31].

Among the limitations of this study are the following: First, the different features of our studies and lack of complete comparability, (for example, in some studies, people had other diseases such as diabetes and metabolic syndrome, and so on). Second: High heterogeneity of research in subgroup analysis. Third: The small number of studies related to HOMA-IR, HBA1C, HDL, LDL, VLDL. Due to the lack of research in this field, it is necessary to conduct stronger research with more samples in this disease.

Declarations

Ethics approval and consent to participate

All the procedures corresponded to the relevant directions of the Committee on Research and Ethics at Shahrekord University, Shahrekord, Iran. This trial was approved by the Ethics Committee of the Sport Sciences Research Center of Iran (IR.SKU.REC.1400.013).

Consent for publication

Not applicable.

Availability of data and materials

The data used to support the findings of this study are included within the article and its supplementary information files

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Mahdi Ghafari, Sajedeh Sadeghiyan, Mohamad Faramarzi, and Timothy Baghurst designed the study. and Maryam Zolfaghari supervised the exercise training protocols. Mahdi Ghafari , Mohammad Faramarzi and Sajedeh Sadeghiyan supervised the data collection procedure. Mahdi Ghafari and Sajedeh Sadeghiyan Masoud Moghaddam wrote the first draft of the manuscript. Timothy Baghurst edited the paper. All authors contributed to the writing of the paper. They also read and approved the final manuscript.

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Figures

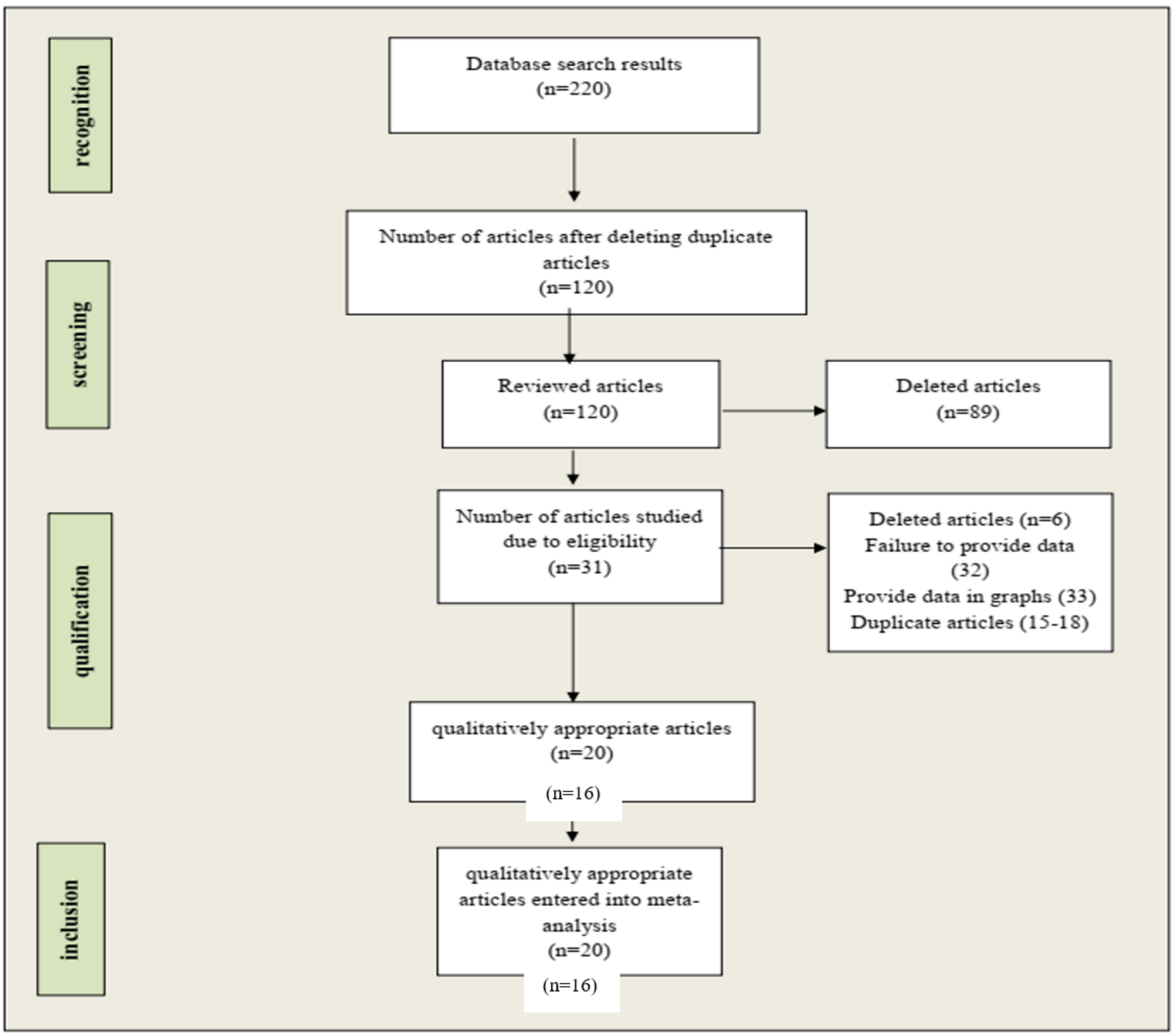

Figure 1

Selection procedure of articles

Figure 2

Quality and risk of bias in meta-analysis studies

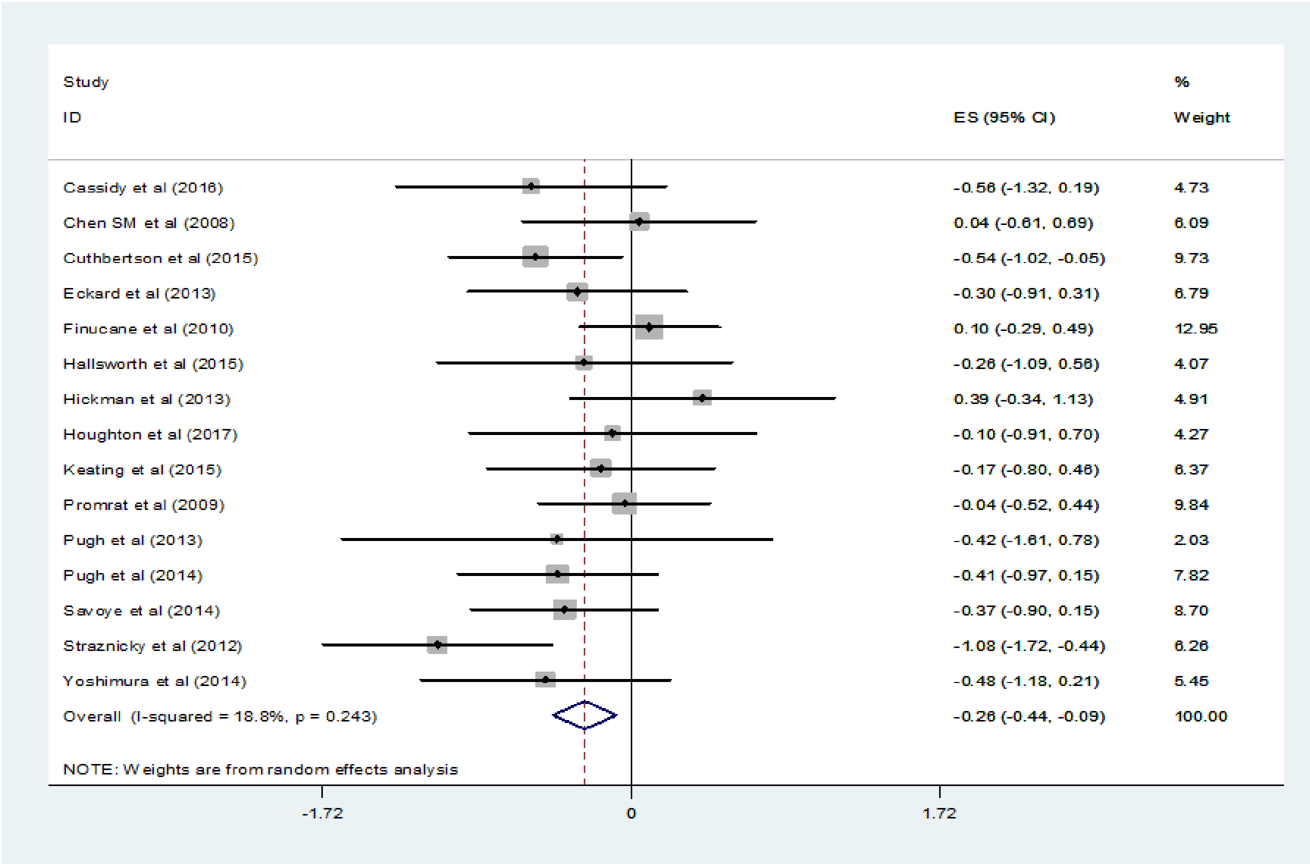

Figure 3

Forest plot of the effect endurance training on glucose levels (P = 0.004, SDM = -0.26, SE = 0.09)

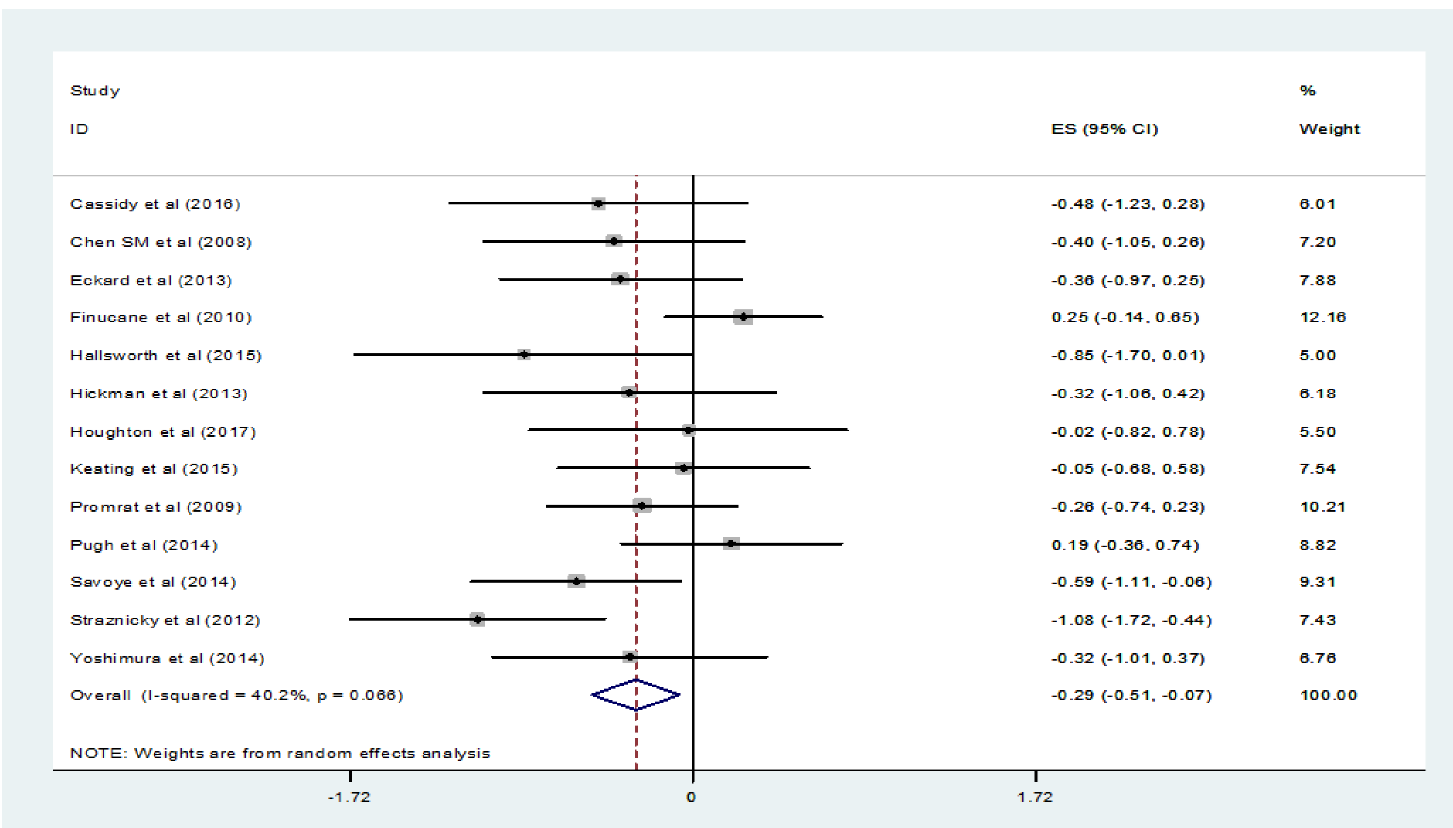

Figure 4

Forest plot of the effect endurance training on insulin levels (P = 0.01, SDM = -0.29, SE = 0.11)

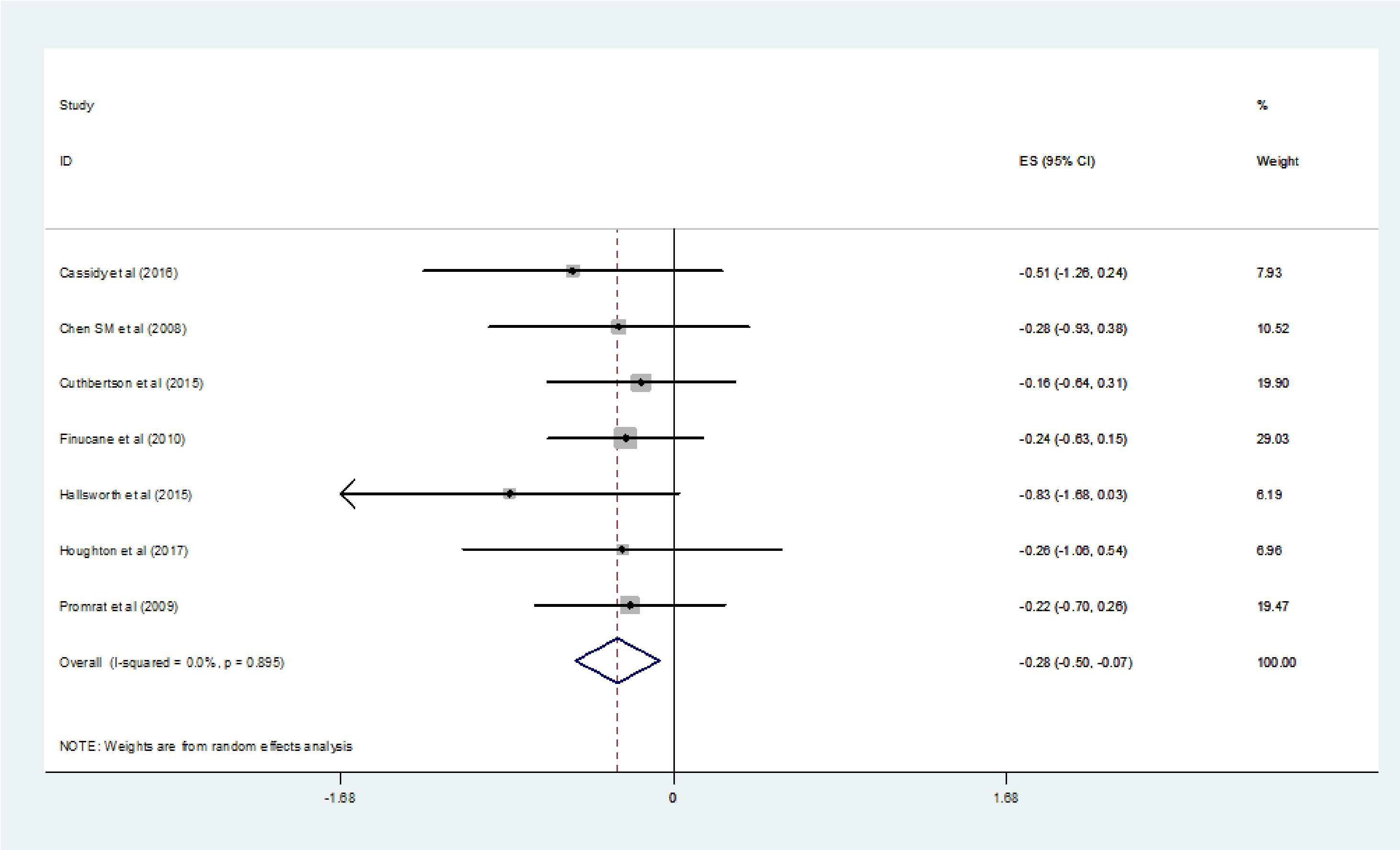

Figure 5

Forest plot of the effect endurance training on HOMA-IR (P= 0.01, SDM=-0.28, SE=0.11)

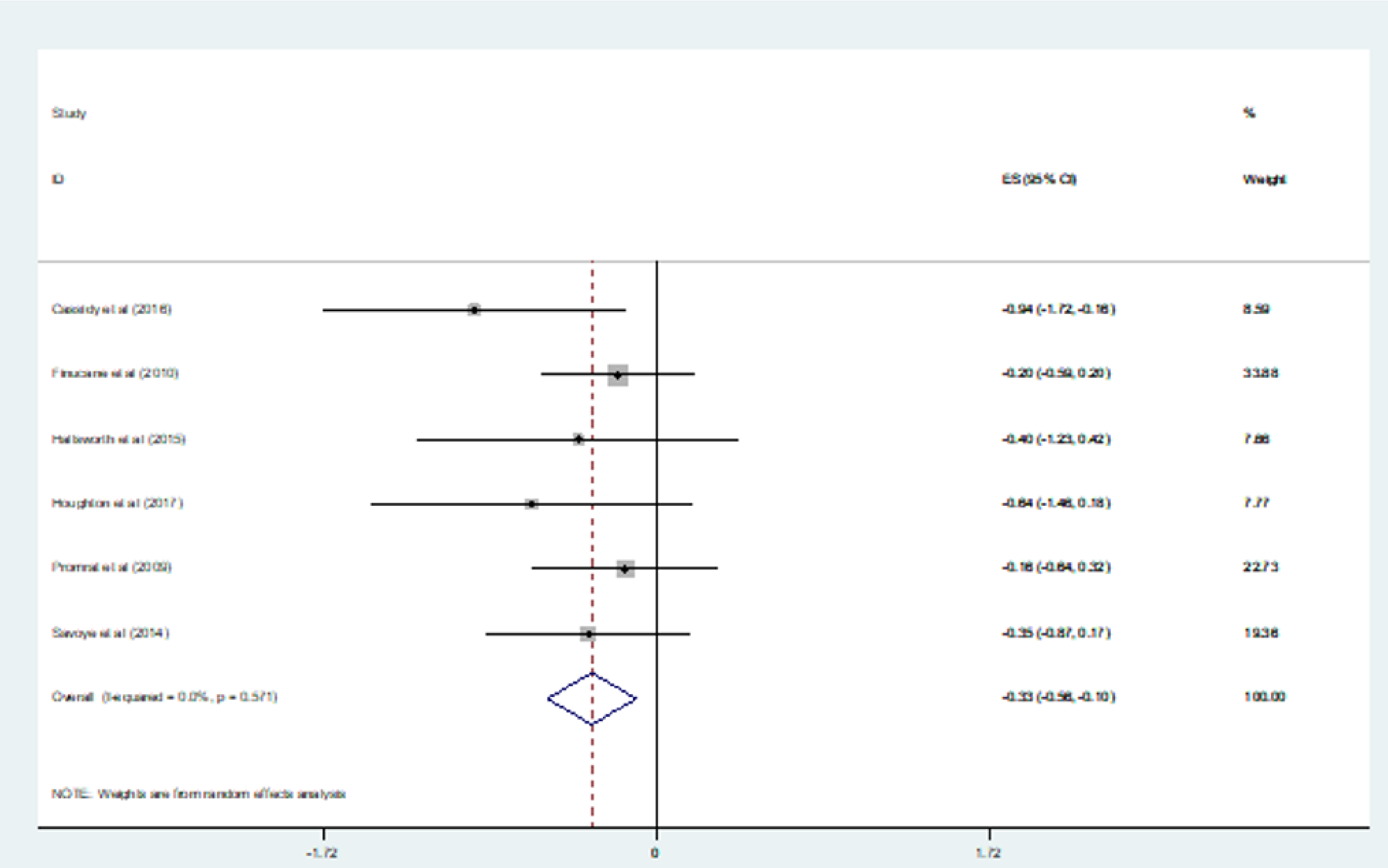

Figure 6

Forest plot of the effect endurance training on Hba1c (P= 0.001, SDM=-0.33, SE=0.12)

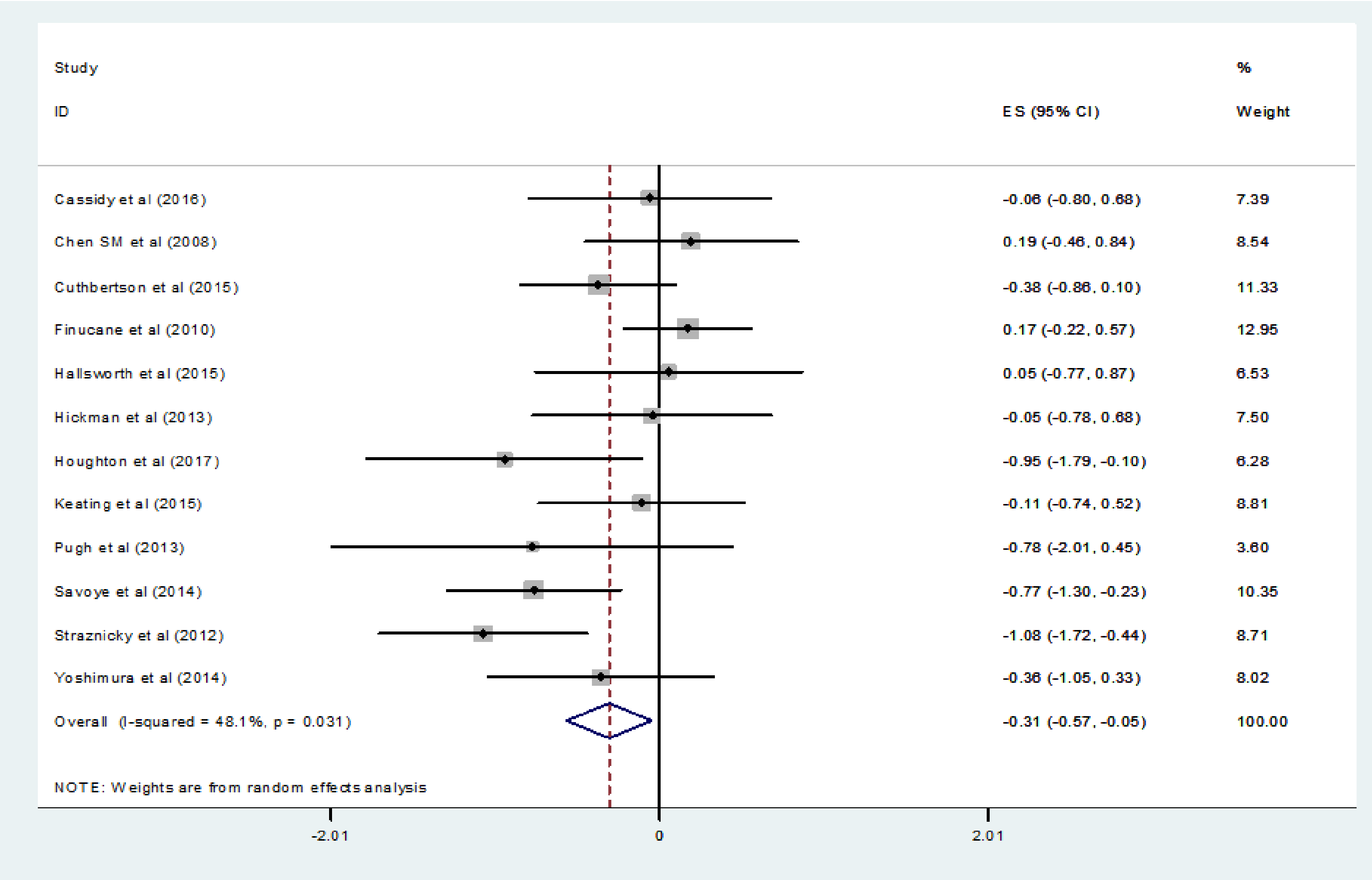

Figure 7

Forest plot of the effect endurance training on Triglyceride (P= 0.02, SDM=-0.31, SE=0.13)

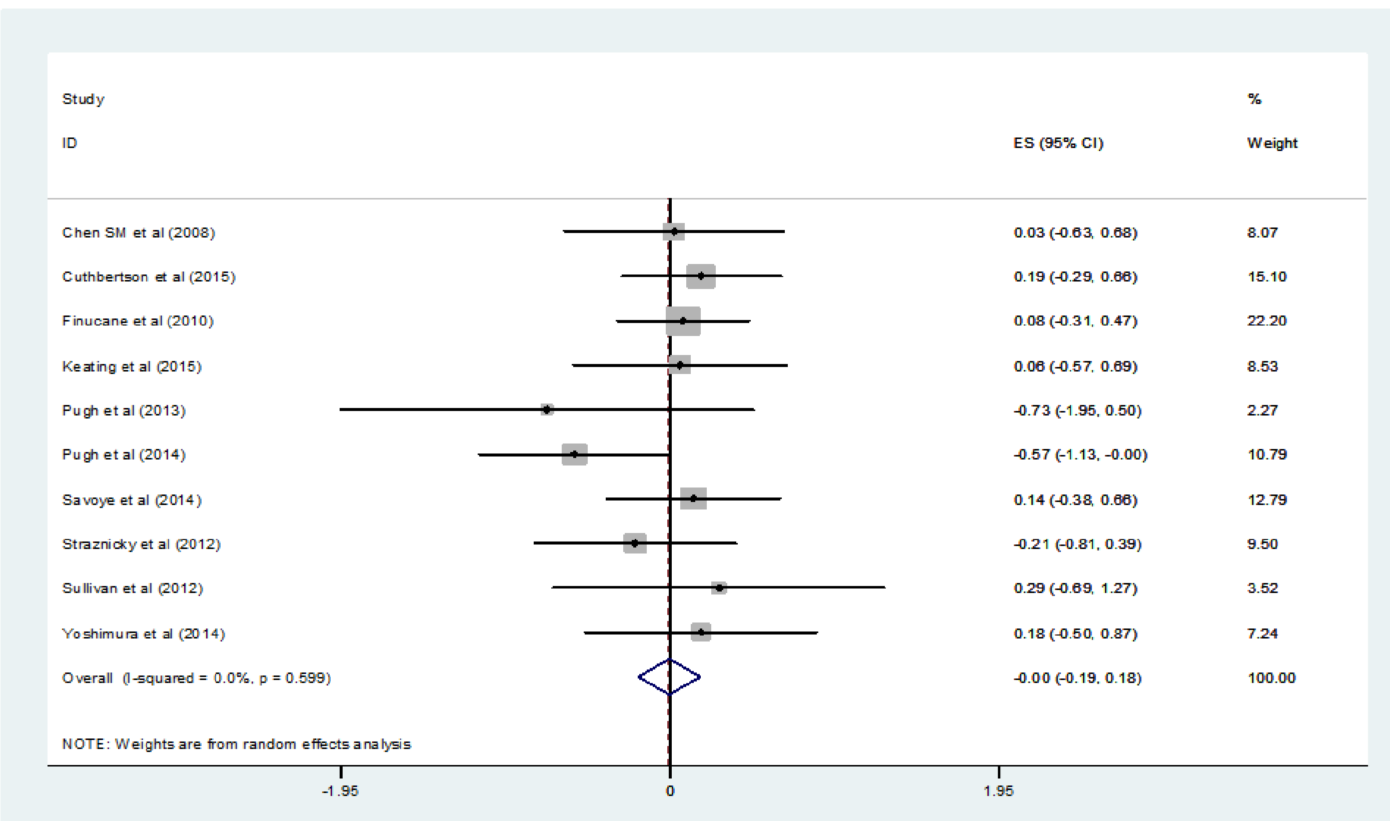

Figure 8

Forest plot of the effect endurance training on HDL levels (P = 0.97, SDM = 0, SE = 0.09)

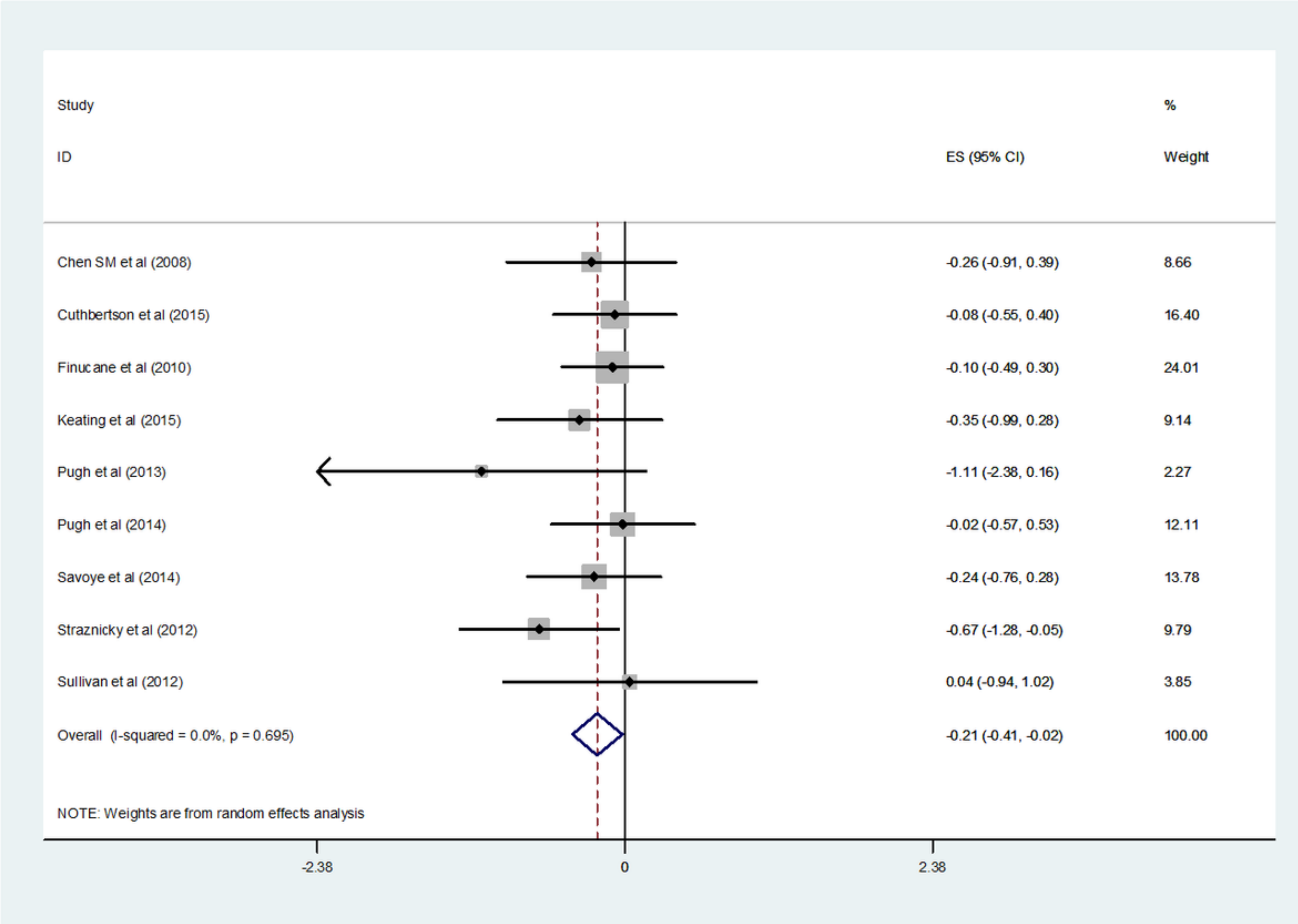

Figure 9

Forest plot of the effect endurance training on LDL levels (P = 0.03, SDM = -0.21, SE = 0.1)