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Review article:

THE EFFECT OF EXERCISE INTERVENTIONS ON IRISIN LEVEL: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

Gholam Rasul Mohammad Rahimi[a], Keyvan Hejazi[b*], Martin Hofmeister[c]

[a] Department of Sports Sciences, Vahdat Institute of Higher Education, Torbat-e-Jam, Iran
[b] Department of Physical Education and Sport Sciences, Hakim Sabzevari University, Sabzevar, Iran
[c] Department Food and Nutrition, Consumer Center of the German Federal State of Bavaria, Munich, Germany

* **Corresponding author:** Keyvan Hejazi, Department of Physical Education and Sport Sciences, Hakim Sabzevari University, Sabzevar, Iran. Tel: +98 (51) 344012620, E-mail: k.hejazi@hsu.ac.ir

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ABSTRACT

Irisin is a hormone that is offered to be a hopeful remedial target in obesity and type 2 diabetes. It has received striking attention recently, whereas, the interactions between exercise training and irisin are still unclear. Therefore, this systematic review and meta-analysis investigated the impacts of exercise interventions on circulating irisin in adults. A systematic search was conducted in PubMed, CINAHL, MEDLINE, Cochrane, Google Scholar, and Scopus up to July 15, 2021. Twenty-four studies, which assessed a total of 921 participants were included and analyzed using a random-effects model to estimate weighted mean differences (MD) with 95 % confidence intervals (CI). Overall, data revealed that exercise training significantly increased circulating irisin (MD: 0.01, 95 % CI: 0.00, 0.01, $p = 0.005$), and declined insulin (MD: -2.09, 95 % CI: -2.81, -1.37, $p < 0.00001$), glucose (MD: -12.89, 95 % CI: -16.52, -9.26, $p < 0.00001$), and insulin resistance (MD: -0.89, 95 % CI: -1.15, -0.62, $p < 0.00001$). Subgroup analysis revealed that irisin raised significantly when resistance training ($p = 0.04$) and combined training ($p = 0.002$) were applied, and for the type 2 diabetes and prediabetes ($p = 0.002$ for both) groups. Moreover, subgroup analysis by the type of intervention demonstrated that insulin reduced when aerobic training ($p < 0.00001$) and combined training ($p = 0.0003$) were employed, but glucose and HOMA-IR reduced after all three types of exercise training. These findings demonstrate that exercise interventions may produce ameliorations in circulating irisin. Further long-term studies are required to confirm these findings.

Keywords: Irisin, exercise intervention, FNDC5, PGC-1α, meta-analysis

INTRODUCTION

Physical activities are among the main factors for health development and prevention of various diseases. It can directly increase energy consumption or indirectly affect the regulation of energy reception and cost of energy through modifying the secretion of the involved hormones (Firth et al., 2020). According to the available findings, exercise training causes morphological and metabolic adaptations such as increased mitochondrial biogenesis (Sanayei et al., 2021) and increased total oxidation capacity in skeletal muscles (Fritzen et al., 2020).

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One of the main properties of physical exercises is transforming white adipose tissue into brown adipose tissue (Verduci et al., 2021). As an endocrine organ, skeletal muscles could release myokines. Numerous studies have shown that exercise training upregulates the expression of peroxisome proliferator-activated receptor-γ coactivator (PGC-1α), demonstrating the potential to activate some genes produced in muscles, such as irisin protein (coded by fibronectin type III domain containing 5 (FNDC5) present in skeletal muscles (Boström et al., 2012). Enhanced expression of FNDC5 in mice leads to a 3-4-fold increase of irisin, which is due to the subcutaneous brown adipose tissue and heat production (Boström et al., 2012; Haas et al., 2012). As a bridge between skeletal muscle and other tissues involved in homeostasis and energy metabolism, including the fatty tissue, irisin is induced by PGC-1α (Boström et al., 2012). Irisin production causes the browning of human and mouse white adipose tissues (Boström et al., 2012), leading to the expression of uncoupling protein 1 (UCP1) (Vliora et al., 2022) and thus, result in enhanced oxidation of fatty acids and heat production. In other words, irisin induces raised heat and energy expenditure, glucose homeostasis, and eventually weight reduction (Boström et al., 2012). PGC-1α is a PPAR-γ transcription factor activator that exerts the major part of its biological effects on energy metabolism (Hosseini et al., 2021). Moreover, it has been illustrated that irisin may mediate some beneficial impacts of exercise in humans, such as mitochondrial biogenesis, angiogenesis, muscle fiber shifting, and preventing muscular atrophy (Jodeiri Farshbaf and Alviña, 2021).

It has been suggested that brown adipose tissue can be utilized as a potential agent for diabetes management, as it ameliorates blood glucose control (Lapa et al., 2017). In this context, experimental data reveal that decreased irisin levels might be associated with increased insulin resistance and glucose tolerance. Clinical studies have also demonstrated a decrease in FNDC5 expression in muscle and subcutaneous adipose tissue (Choi et al., 2013). Furthermore, various studies have reported a lower serum level of irisin in type 2 diabetes patients versus healthy individuals (Choi et al., 2013; Zhang et al., 2016). Therefore, irisin may have utility as a preventive agent to tackle obesity and metabolic diseases (Arhire et al., 2019).

To date, little is known about the type of exercise training needed to produce phenotypic changes in adipose tissue to improve health. Although recent studies have shown that the increased irisin levels due to physical exercise are associated with signs of decreased metabolic syndrome and insulin resistance (Elizondo-Montemayor et al., 2018), there are contradicting results concerning the outcomes of exercise interventions on the conversion of white adipose tissue to brown adipose tissue and their role in the prevention of obesity. For instance, a 2015 systematic review by Qiu et al. (2015) studied the impacts of long-term exercise on circulating irisin in adults; the results revealed that chronic resistance training had a moderate and significant effect in reducing irisin compared with the control group, while endurance exercise only had a trend toward significance. By contrast, a 2018 systematic review by Fox et al. (2018) investigated the effect of an acute bout of exercise on the magnitude of post-exercise circulating irisin in adults; the authors concluded that irisin concentration increases substantially immediately after an acute bout of exercise. Furthermore, the recent systematic review by Cosio et al. (2021) examined the efficacy of chronic resistance training on circulating irisin in adults. Data suggested that resistance training regimens seemed to elevate circulating irisin, especially in older adults and in demanding and progressive training interventions.

Although many studies are being conducted on irisin, the physiological functions of this myokine in humans and the effects of various exercise training on its expression are still ambiguous (Nygaard et al., 2015). In addition, the limited number of high-quality

trials directly investigating different modes of physical exercise regimens prevents any judgments on the most efficient influence on irisin. As a result, before recommending exercise programs as a non-pharmacological therapeutic measure and providing a final opinion on its positive impacts, the need for additional investigations seems necessary (Norheim et al., 2014; Oelmann et al., 2016).

Four meta-analyses on exercise training efficacy on irisin levels were conducted previously (Cosio et al., 2021; Jandova et al., 2021; Motahari Rad et al., 2021; Qiu et al., 2015); nevertheless, their participants' range of age (Jandova et al., 2021) and level of physical activity (Motahari Rad et al., 2021; Qiu et al., 2015), and type of intervention (Cosio et al., 2021) differed from the current meta-analysis. Moreover, both non-randomized and randomized controlled trials (RCTs) were included in these reviews (Jandova et al., 2021; Qiu et al., 2015). Therefore, the current review aimed to synthesize the pooled data from RCTs and controlled trials to examine the efficacy of exercise training regimens for changing circulating irisin and insulin resistance in adults.

METHODS

Search strategy

A detailed search was performed using five databases, including PubMed, CINAHL, and Medline, Google Scholar, and Scopus. Searches included a mix of medical subject headings and free-text terms associating with the keywords "irisin", "FNDC5", "exercise training", "resistance training", "aerobic training", "strength training", "walking", "combined aerobic and resistance training", "circuit training", "circuit weight training", "interval training", "chronic exercise", "myokines", and "physical activity". The Boolean search terms (AND, OR, or NOT) were used, we merged the search terms; exercise training participation with the term irisin and/or FNDC5. The search strategy covered the period from database inception until July 15, 2021. Then, following the initial screening, systematic reviews, meta-analyses, and all study references were also searched to ensure that all relevant articles established on a basis on the inclusion and exclusion criteria. The current study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021).

Selection criteria

The participants, intervention, comparison, outcome, time, and study design (PICOTS) criteria were considered to determine the study inclusion criteria. The titles, abstracts, and full text were independently reviewed by two investigators to appropriate articles to establish study eligibility. Exercise training RCTs and controlled trials in adults were included. In the current meta-analyses, exercise interventions comprised aerobic, resistance, and combined (aerobic + resistance) training. Studies included in this review compared adults in the intervention and control groups.

Inclusion/exclusion criteria

To study identification and selection, we used the criteria as follows: 1) full-text RCTs or control trials published in the English language; 2) adults (aged ≥ 18 years); 3) investigations that used aerobic, resistance, or combined aerobic and resistance training, in a pre-post design with a non-exercise control group; 4) studies reported circulating (plasma/serum) irisin levels. Review articles, literature reviews, conferences, abstracts, and study protocols have been omitted.

Outcome measures

The primary outcome was plasma/serum irisin level (in µg/mL), which was measured using a standardized commercial Enzyme-Linked Immunosorbent Assay (ELISA) kit. The secondary outcome measures were fasting glucose (in mg/dl), insulin (in mcUI/mL), and HOMA-IR.

Data extraction

Two authors (GRMR and KH) individually extracted the data, and disagreements

between us were resolved by discussion. The information extracted comprised author, year of publication and country, the number of cases and controls, mean age of participants, health status, features of the exercise programs, mean and standard deviation (SD) of the outcome measures at baseline, post-intervention and/or changes between baseline and post-intervention.

Data synthesis

The effect size of any outcomes was summarized by calculating the mean difference (MD) between the exercise intervention and control condition from pre-intervention and post-intervention for all included papers. We evaluated and detailed independently any result if each research reported different results for the current study. Given similar reporting techniques for outcomes, the mean difference (MD) with 95 % confidence interval (CI) was applied. Review Manager 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark) was employed for performing all analyses. Extracted outcome data were completed by the change in the mean and SD values.

The mean at baseline was subtracted from the post-intervention mean, and the change SD was computed using for study group participant numbers in conjunction with group p-values or 95 % CI where the change in mean and SD was not reported. In articles that reported standard error of the mean (SEM) data instead of the SD, this value was converted to SD (Higgins et al., 2003). Where data were not presented in text or tables, and authors could not be contacted, data revealed in figures were extracted or obtained where feasible by GetData Graph Digitizer software. Where an article contained a control group and more than one exercise group, we separately labeled each exercise group and divided the sample size of the control group by the number of exercise groups.

Pooled estimates of the effect of exercise on outcome measures were obtained using a random-effects model. The heterogeneity among the studies was evaluated by the I2 statistic, with values >50 % considered to show substantial heterogeneity (Higgins et al., 2003). Subgroup analyses were employed to recognize potential causes of heterogeneity among the studies. Exercise training modality (aerobic, resistance, combined aerobic and resistance), health status (e.g., patients with multiple sclerosis, type 2 diabetes, and metabolic syndrome), body mass index classification (BMI < 25 kg/m^2, or ≥ 25 kg/m^2), and gender were considered as the predefined sources of heterogeneity. Meta-analysis was carried out using Forest plots and used a 5 % level of significance to reveal the significance of results. The risk of publication bias was assessed employing Funnel plots (Egger et al., 1997), considering $p < 0.05$ a statistically significant bias.

Study quality

The methodological quality of the investigations was examined independently based on a fifteen-point scale, Tool for the Assessment of Study Quality and Reporting in Exercise (TESTEX), which is a validated tool for evaluating the quality (5 points maximum) and reporting (10 points maximum) of exercise training studies (Smart et al., 2015). Two independent reviewers (GhRMR and KH) conducted this evaluation, and any disagreements between us were resolved by consensus.

RESULTS

Study and participant characteristics

One thousand one hundred and thirty-one records were identified in the initial search. After removing duplicates and animal researches (n = 947), the remaining papers were screened based on the title and the abstract, and then 145 articles were omitted, leaving 39 full-text articles. Fifteen other articles were removed because of the following reasons: (a) did not include control group (Brinkmann et al., 2022; Dünnwald et al., 2019; Norheim et al., 2014; Otero-Díaz et al., 2018; Rashid et al., 2020; Sari-Sarraf et al., 2017; Tsuchiya et al., 2015; Winn et al., 2017), (b) participants with mean age <18

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years (Archundia-Herrera et al., 2017; Blizzard LeBlanc et al., 2017; Dundar et al., 2021), (c) acute trials (a training period less than two weeks or performing only an acute exercise testing) (Kraemer et al., 2014; Tsuchiya et al., 2014), (d) lack of access to data (Hecksteden et al., 2013; Micielska et al., 2019). Twenty-four articles (Amanat et al., 2020; Azimi Rashti et al., 2019; Bagheri et al., 2020; Banitalebi et al., 2019; Bonfante et al., 2017; Briken et al., 2016; Dianatinasab et al., 2020; Enteshary et al., 2019; Ghanbari-Niaki et al., 2018; Jafari et al., 2020; Jaffari et al., 2020; Kim et al., 2016; Korkmaz et al., 2019; Miyamoto-Mikami et al., 2015; Motahari Rad et al., 2020; Murawska-Cialowicz et al., 2020; Nazari et al., 2017; Pekkala et al., 2013; Poutafkand et al., 2020; Rezaeimanesh, 2020; Safarimosavi et al., 2021; Scharhag-Rosenberger et al., 2014; Tofighi et al., 2017; Zhao et al., 2017) met our inclusion criteria and were entered in the meta-analysis (PRISMA flow diagram; Figure 1). Studies were carried out in Iran (15), Germany (2), Finland (2), Japan (1), Poland (1), South Korea (1), China (1), and Brazil (1). The 24 included articles had 921 subjects, 590 (64 %) subjects in the intervention group, and 331 (36 %) in the control group.

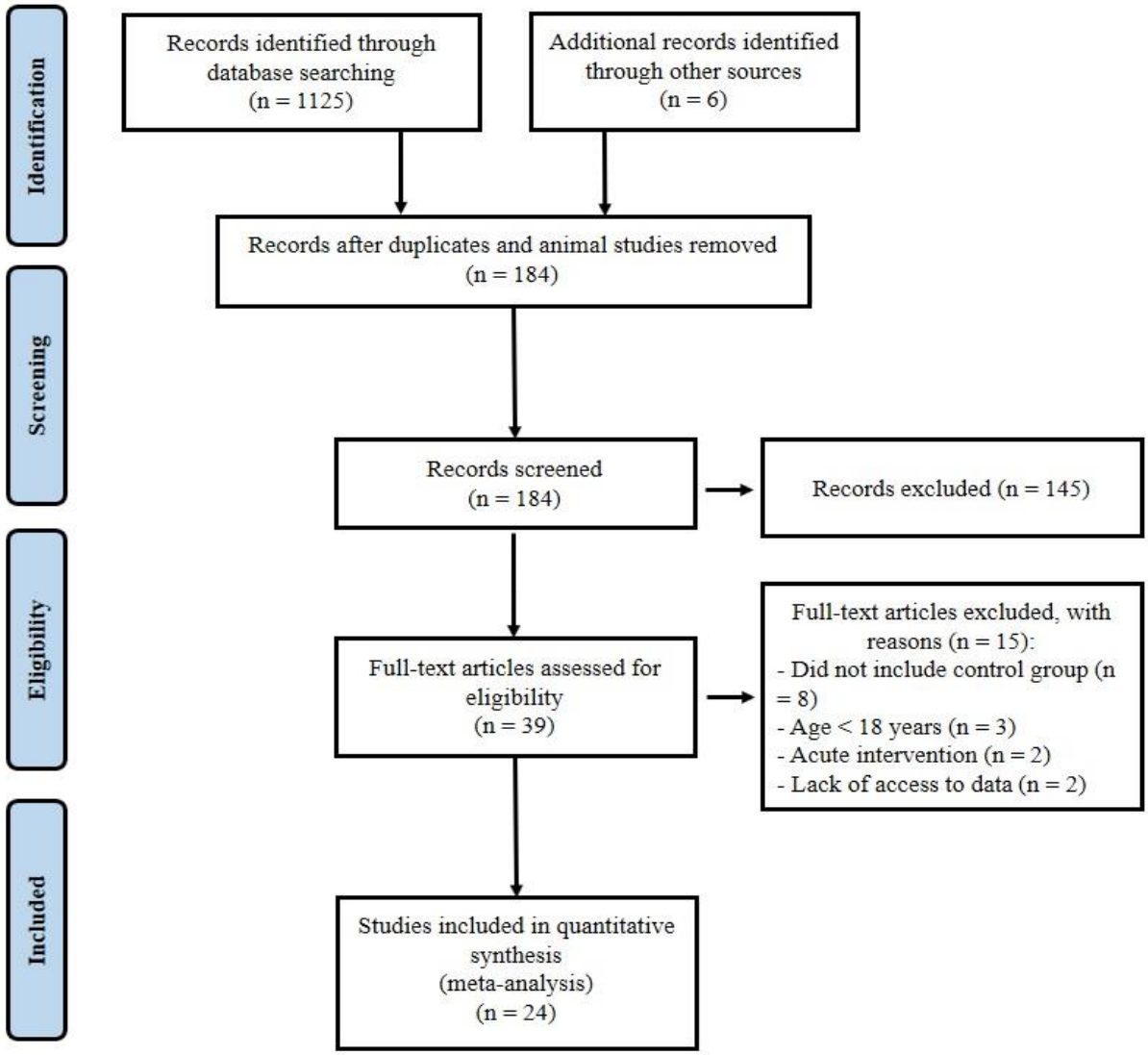

Figure 1: PRISMA flow diagram

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Intervention details

The relevant characteristics for each of the included studies are provided in Supplementary Table 1. The intervention period of studies varied from 8 to 24 weeks, with each session's length of range 15–90 min. Twelve studies exclusively recruited male subjects (Bagheri et al., 2020; Bonfante et al., 2017; Jafari et al., 2020; Jaffari et al., 2020; Korkmaz et al., 2019; Motahari Rad et al., 2020; Murawska-Cialowicz et al., 2020; Nazari et al., 2017; Pekkala et al., 2013; Rezaeimanesh, 2020; Safarimosavi et al., 2021; Zhao et al., 2017), eight studies exclusively recruited female subjects (Amanat et al., 2020; Azimi Rashti et al., 2019; Banitalebi et al., 2019; Dianatinasab et al., 2020; Enteshary et al., 2019; Ghanbari-Niaki et al., 2018; Poutafkand et al., 2020; Tofighi et al., 2017), and four studies recruited both males and females (Briken et al., 2016; Kim et al., 2016; Miyamoto-Mikami et al., 2015; Scharhag-Rosenberger et al., 2014). In 22 studies, the mean age of subjects varied from 22.5 to 62.1 years. Two studies (Miyamoto-Mikami et al., 2015; Rezaeimanesh, 2020) did not report the mean age of participants. Based on BMI classification criteria, four investigations had subjects who were classified on average as obese, 14 as overweight, four as the normal weight, with two not reporting mean BMI (Briken et al., 2016; Enteshary et al., 2019). Studies specifically recruited participants with type 2 diabetes (three investigations), metabolic syndrome (two investigations), obese-only subjects (five investigations), overweight subjects (seven investigations), or both obese and overweight (two investigations). One investigation recruited exclusively for prediabetes and one for multiple sclerosis.

Three studies employed aerobic exercise training, four studies investigated resistance training, four studies examined isolated aerobic and resistance training, two studies used all three modalities (aerobic, resistance, and combined aerobic + resistance training), three studies employed high-intensity interval training, and two studies examined isolated high-intensity interval training and continuous endurance training. Moreover, one study used isolated aerobic and combined aerobic + resistance training, two studies reviewed combined aerobic + resistance training, one study employed isolated high-intensity interval training and moderate-intensity interval training, one study used isolated sprint interval training and combined aerobic + resistance training and one study employed isolated resistance training + high-intensity interval training and resistance training + moderate-intensity continuous training.

Meta-analysis results

Change in irisin

Based on 40 intervention arms, exercise interventions significantly increased irisin [0.01 µg/mL (95 % CI, 0.00 to 0.01), p = 0.005] when compared with a control group (Figure 2). There was a significant moderate heterogeneity (I^2 = 75 %, p < 0.00001) among studies included for this comparison.

Subgroup analysis by exercise training modalities revealed a significant increase in irisin for studies with resistance [0.01 µg/mL (95 % CI, 0.00 to 0.02), p = 0.04; I^2 = 79 %, p < 0.00001; 22 interventions] and combined aerobic + resistance [0.00 µg/mL (95 % CI, 0.00 to 0.01), p = 0.002; I^2 = 0 %, p = 0.72; six interventions] protocols, but not for studies with aerobic training protocols [-0.01 µg/mL (95 % CI, -0.03 to 0.02), p = 0.60; I^2 = 70 %, p = 0.0001; 12 interventions].

Subgroup analyses by health status of participants revealed a significant change in irisin for patients with type 2 diabetes [0.00 (95 % CI, 0.00 to 0.01), p = 0.002; I^2 = 0.0 %; six interventions] and prediabetes [-0.06 (95 % CI, -0.10 to -0.02), p = 0.002. I^2 = 40 %; three interventions]. In investigations that included metabolic syndrome populations, however, there was not a significant change reported for irisin [0.45 (95 % CI, -0.08 to 0.99), p = 0.10; I^2 = 0.0 %; six interventions].

In addition, subgroup analyses by BMI and gender did not reveal any significant effects (see Supplementary Table 2).

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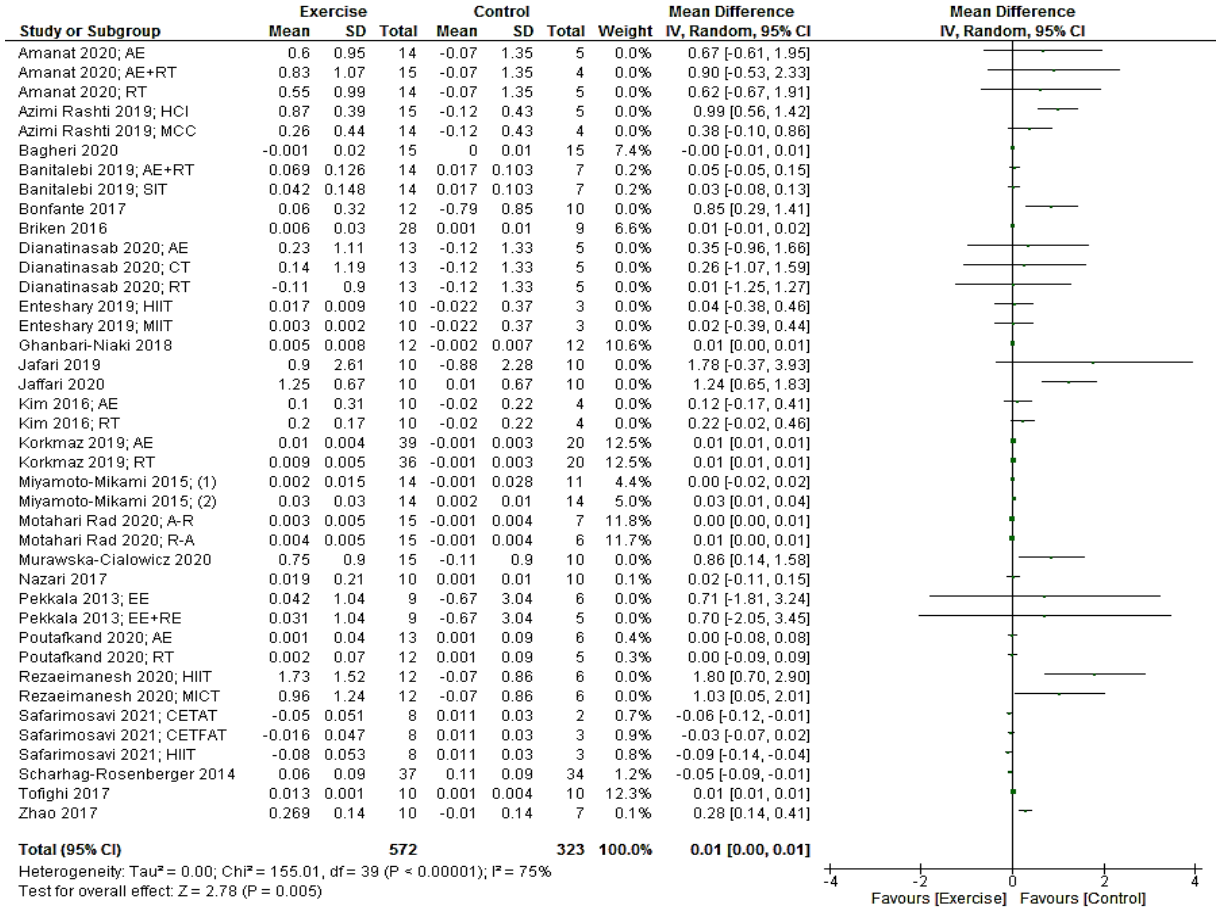

Figure 2: Forest plot of the effects of exercise training versus control on irisin. AE, aerobic; RT, resistance training; HCI, high-intensity concurrent interval; MCC, moderate-intensity concurrent continues; SIT, sprint interval training; HIIT. High intensity interval training; A-R, aerobic-resistance; R-A, resistance-aerobic; EE, endurance exercise; CETFAT, continuous endurance training with intensity equivalent to Fatmax (maximal fat oxidation); CETAT, continuous endurance training with intensity equivalent to anaerobic threshold

Change in fasting insulin, fasting glucose, and insulin resistance

Eighteen arms providing a total of 307 participants reported fasting insulin as an outcome measure. Pooled results from the random-effects model revealed that exercise training significantly decreased insulin levels (MD: -2.09 mcUI/mL; 95 % CI [-2.81, -1.37]; p < 0.00001). When we stratified studies based on the mode of exercise training (aerobic, resistance, and combined), we found a significant reduction in insulin after aerobic (MD: -2.43 mcUI/mL; 95 % CI [-3.58, -1.28]; p < 0.0001; 11 interventions) and combined (MD: -2.02 mcUI/mL; 95 % CI [-3.12, -0.92]; p = 0.0003; four interventions) training, but not after resistance training (MD: -1.07 mcUI/mL; 95 % CI [-2.21, 0.08]; p = 0.07; three interventions) (Figure 3).

Eight studies (18 arms) presenting a total of 319 participants reported fasting glucose as an outcome measure. Pooled results showed that glucose levels reduced in the intervention group compared with the control group (MD: -12.89 mg/dL; 95 % CI [-16.52, -9.26]; p < 0.00001). Subgroup analyses by the mode of exercise training revealed a significant reduction for studies with aerobic (MD: -13.59 mg/dL; 95 % CI [-18.12, -9.05]; p < 0.00001; 11 arms), resistance (MD: -7.44 mg/dL; 95 % CI [-14.62, -0.27]; p = 0.04; three arms), and combined (MD: -15.00 mg/dL; 95 % CI [-26.6, -3.37]; p = 0.01; four arms) training (Figure 4).

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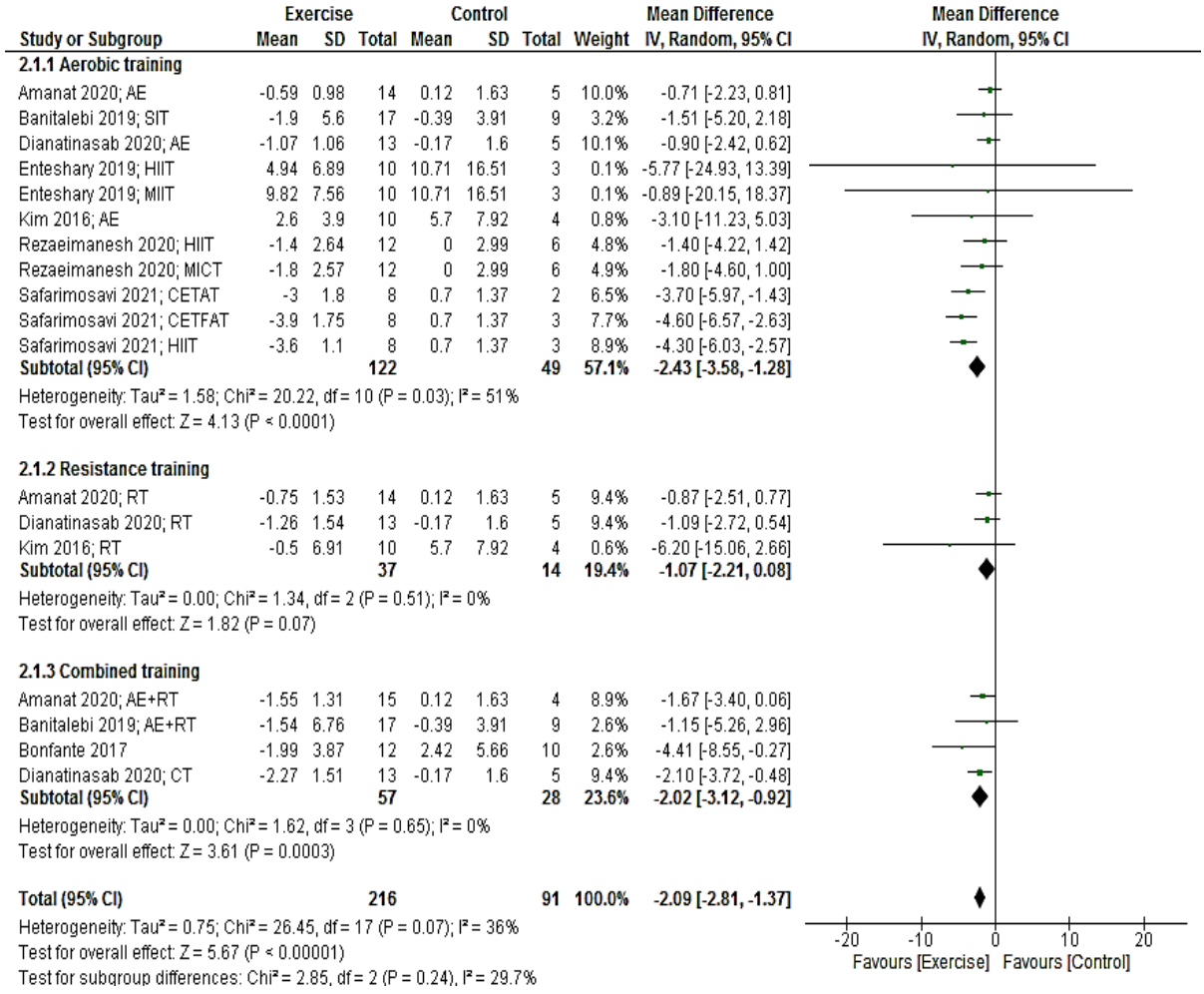

Figure 3: Forest plot of the effects of exercise training versus control on insulin. AE, aerobic; RT, resistance training; SIT, sprint interval training; HIIT. High intensity interval training; CETFAT, continuous endurance training with intensity equivalent to Fatmax (maximal fat oxidation); CETAT, continuous endurance training with intensity equivalent to anaerobic threshold

Eight studies (18 arms) providing a total of 324 participants reported HOMA-IR as an outcome measure. Pooled results presented that HOMA-IR reduced in the intervention group compared with the control group (MD: -0.89; 95 % CI [-1.15, -0.62]; p < 0.00001).

Subgroup analyses by the mode of exercise training revealed a significant reduction for studies with aerobic (MD: -0.98; 95 % CI [-1.33, -0.63]; p < 0.00001; 10 arms), resistance (MD: -50; 95 % CI [-0.95, -0.05]; p = 0.03; three arms) and combined (MD: -0.92; 95 % CI [-1.56, -0.27]; p = 0.005; five arms) training (Figure 5).

Study quality

The overall methodological quality of included studies was estimated to be moderate to good, with a median TESTEX score of 9 (range 7–12) out of a maximum of 15. Two investigations scored 12, one study scored 11, five experiments scored 10, seven experiments scored 9, six experiments scored eight and three experiments scored 7 (see Supplementary Table 3). Of the TESTEX criteria, the following was done particularly poorly: physical activity monitoring in the control groups 0/24; intention to treat analyses only 1/24 study; allocation concealment only 4/24 studies; randomization specified 9/24 studies. The other criteria were each met in at least 50 % of investigations.

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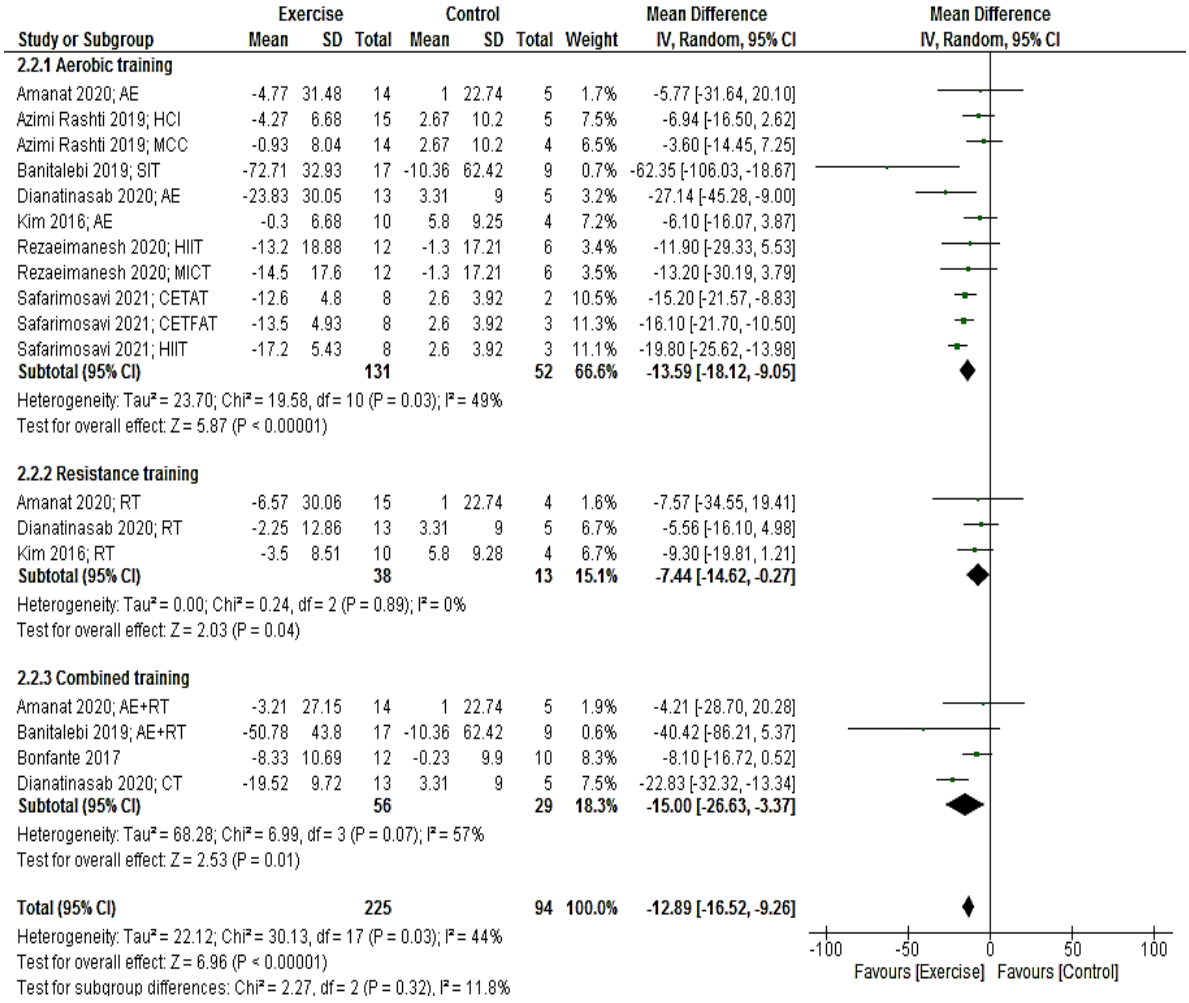

Figure 4: Forest plot of the effects of exercise training versus control on glucose. AE, aerobic; RT, resistance training; SIT, sprint interval training; HIIT. High intensity interval training; CETFAT, continuous endurance training with intensity equivalent to Fatmax (maximal fat oxidation); CETAT, continuous endurance training with intensity equivalent to anaerobic threshold

Heterogeneity and publication bias

Our analyses demonstrated high heterogeneity in irisin (I^2 = 75 %, p < 0.00001) and moderate heterogeneity in HOMA-IR (I^2 = 51 %, p = 0.007), fasting glucose (I^2 = 44 %, p = 0.03), and fasting insulin (I^2 = 36 %, p = 0.07). Egger plots exhibited little to moderate evidence of publication bias as the standard error/mean difference plots were tightly grouped together (see Supplementary Figures 1–4).

DISCUSSION

The current meta-analysis included published randomized controlled trials (RCTs) investigating the efficacy of exercise training in circulating irisin and insulin resistance in adults. Based on 24 studies comprised of 40 intervention arms, exercise intervention significantly increased irisin compared with a control condition. Subgroup analysis by exercise training modalities revealed a significant increase in irisin for studies with resistance and combined aerobic + resistance protocols, but not for studies with aerobic training. Moreover, subgroup analyses by the health status of participants revealed a significant change in irisin for patients with type 2 diabetes and prediabetes. Investigations included metabolic syndrome populations, however, did not show a substantial alteration in irisin.

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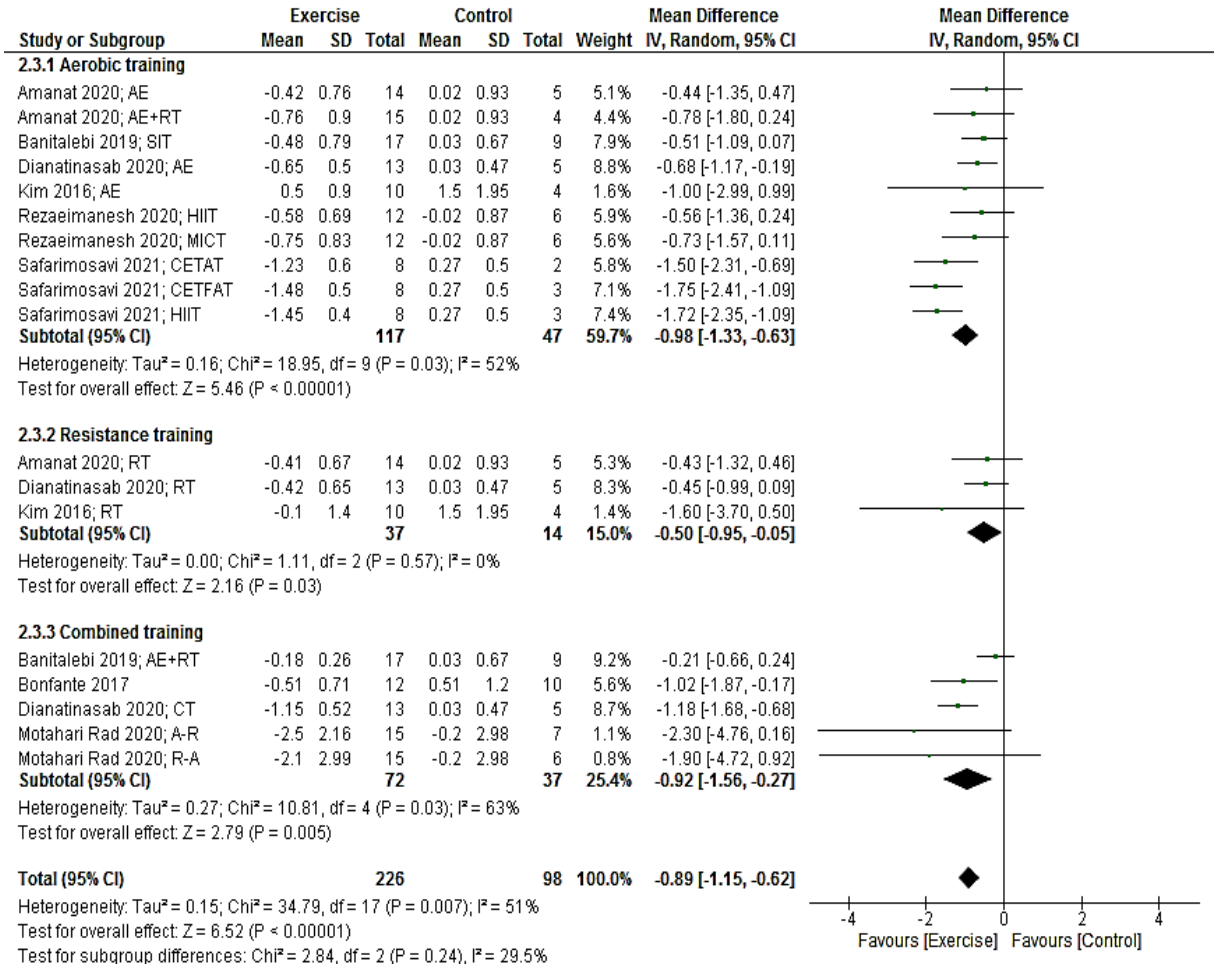

Figure 5: Forest plot of the effects of exercise training versus control on HOMA-IR. AE, aerobic; RT, resistance training; SIT, sprint interval training; HIIT. High intensity interval training; CETFAT, continuous endurance training with intensity equivalent to Fatmax (maximal fat oxidation); CETAT, continuous endurance training with intensity equivalent to anaerobic threshold

As a hormone derived from FNDC5, irisin is recognized as the target gene for PGC1-α. mRNA FNDC5 is expressed higher in muscles than in other organs (Huh et al., 2012), and the increased expression of FNDC5 in skeletal muscles is significantly linked to the serum level of irisin (Huh et al., 2012; Roca-Rivada et al., 2013). Studies have displayed a robust association between muscle levels of mRNA FNDC5 and FNDC5 (Lecker et al., 2012; Norheim et al., 2014), supporting the role of PGC1-α as a regulator for FNDC5 and irisin. However, perhaps the isolated resistance and mixed aerobic + resistance interventions have induced the activation of effective signaling on the up-regulation of PGC1-α (Suwa et al., 2008), resulting in FNDC5 expression and then elevation in circulating irisin. It has been reported that there is a correlation between changes in irisin concentration and lactate, both increments following physical activities, and it is suggested that the increase in irisin is due to muscle needs. A hypothesis states that muscle need might play a role in irisin's physiological regulation (Daskalopoulou et al., 2014); the rise in irisin after acute exercise is associated with diminished muscular ATP level. There is the possibility that diminished ATP or increased ADP level in addition to phosphate group might activate irisin signaling to help store ATP homeostasis in muscular function (Huh et al., 2012). Irisin level is correlated with the amount of

ATP in the first place and with metabolites related to glycolysis and lipolysis in the skeletal muscle in the second place (Huh et al., 2012). Engagement in exercise training leads to a further reduction in muscles' creatine phosphate, ATP, and glycolysis (Hargreaves et al., 1998). While these exercises increase the activity of AMP-activated protein kinase, which per se activates PGC1-α and phosphorylation (Jäger et al., 2007; Knutti et al., 2001). In the present study, the reduction in ATP and increased activation of PGC1-α due to exercise training probably leads to the release of irisin from its primary source, skeletal muscle FNDC5, into the bloodstream. Part of these differences between various types and intensities of exercises are probably because of intracellular energy levels. In fact, it has been shown that conducting workouts at high intensity leads to increased AMP, ADP, AMP/ATP ratio, and lactate versus workouts at low intensity (Chen et al., 2003). Moreover, the relationship between irisin and intracellular metabolites (Huh et al., 2012), may partially explain the difference between various types of physical exercises on its level. Physiologically, it is unclear if raised serum level of FNDC5-derived irisin is in response to exercise training, or FNDC5 is stored before translation, or its raised serum level is because of increased muscle need. Alternatively, physical exercises might activate the breakdown of specific factors derived from FNDC5, leading to the rapid release of irisin into the bloodstream at the beginning of activity (Daskalopoulou et al., 2014). The study by Norheim et al. (2014) stated that the plasma level of irisin is probably independent of an increase in FNDC5. Nevertheless, further research is required to confirm the mechanisms underlying the impact of exercise training on irisin.

Our results illustrate that insulin, glucose, and insulin resistance significantly reduced after exercise interventions. When we stratified studies based on the mode of exercise training (aerobic, resistance, and combined), we found a significant reduction in insulin after aerobic and combined training, but not after resistance training. Subgroup analyses by the mode of exercise training revealed a considerable reduction of glucose and insulin resistance for studies with aerobic, resistance, and combined training. A number of recent meta-analyses reported that exercise training had a moderate-to-large impact on reducing glucose, insulin, and HOMA-IR in adults (Ashton et al., 2020; Kumar et al., 2019; Mohammad Rahimi et al., 2021). Some mechanisms that could increase the function of insulin after aerobic exercises include increased insulin post-receptor signaling, increased expression of insulin-responding glucose transporter 4 (GULT4), increased activity of glycogen synthetase and hexokinase, decreased release and increased removal of free fatty acids, increased release of glucose from the blood into muscles due to increased muscular capillaries and the modified combination of muscles to increase glucose uptake (Eriksson et al., 1997). Therefore, aerobic exercises are methods to decrease insulin resistance and the risk for developing type 2 diabetes, particularly in obese individuals. Insulin resistance may potentially be mediated by changes in the function of several peptide mediators secreted from adipocytes, including tumor necrosis factor-alpha (TNFα), leptin, and adiponectin (Alizaei Yousefabadi et al., 2021). In non-inflammatory conditions, TNFα is derived from adipose tissue, and its plasma level is associated with body fatty tissue. TNFα interferes with insulin signaling by reducing signaling through serine phosphorylation. Adiponectin is secreted from adipocytes with an inverse proportion to adipocytes, and it is a potential TNFα inhibitor. The serum level of adiponectin decreases in obesity, insulin resistance, diabetes mellitus, and metabolic syndrome (Das, 2010). Another reason for these contradicting findings could probably be due to differences in the duration, intensity, and exercise level of the subjects.

The strength of this meta-analysis is that we pooled all included studies in our analysis and compared the impact of various types

of exercise training on circulating irisin and metabolic outcome measures; however, we acknowledge that there are some limitations to our findings. The existing sample size, similar to many other analyses on the effects of exercise training, was small, thereby restricting the generalizability of our results. Second, exercise intensity, duration, and period of the interventions varied substantially in the employed studies, which may have impacted our results. Third, in the main meta-analysis, there were small-study effects that could be attributed to the bias of publication, poor methodological quality, true heterogeneity, and chance (Higgins, 2011).

CONCLUSION

Our study displays that exercise training intervention may help improve irisin levels in adults, especially in type 2 diabetes and prediabetes patients. Moreover, isolated resistance exercise and combined aerobic and resistance exercise appear to be optimal in changes of irisin. Future studies are needed to clarify the mechanisms underlying the impact of exercise training on irisin in adults.

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Conflict of interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

Alizaei Yousefabadi H, Niyazi A, Alaee S, Fathi M, Mohammad Rahimi GR. Anti-inflammatory effects of exercise on metabolic syndrome patients: a systematic review and meta-analysis. Biol Res Nurs. 2021;23: 280-92.

Amanat S, Sinaei E, Panji M, MohammadporHodki R, Bagheri-Hosseinabadi Z, Asadimehr H, et al. A randomized controlled trial on the effects of 12 weeks of aerobic, resistance, and combined exercises training on the serum levels of nesfatin-1, irisin-1 and HOMA-IR. Front Physiol. 2020;11:562895.

Archundia-Herrera C, Macias-Cervantes M, Ruiz-Muñoz B, Vargas-Ortiz K, Kornhauser C, Perez-Vazquez V. Muscle irisin response to aerobic vs HIIT in overweight female adolescents. Diabetol Metab Syndr. 2017;9:101.

Arhire LI, Mihalache L, Covasa M. Irisin: a hope in understanding and managing obesity and metabolic syndrome. Front Endocrinol. 2019;10:524.

Ashton RE, Tew GA, Aning JJ, Gilbert SE, Lewis L, Saxton JM. Effects of short-term, medium-term and long-term resistance exercise training on cardiometabolic health outcomes in adults: systematic review with meta-analysis. Br J Sports Med. 2020;54:341-8.

Azimi Rashti B, Mehrabani J, Damirchi A, Babaei P. The influence of concurrent training intensity on serum irisin and abdominal fat in postmenopausal women. Przeglad menopauzalny= Menopause review. 2019;18: 166-73.

Bagheri R, Rashidlamir A, Ashtary-Larky D, Wong A, Grubbs B, Motevalli MS, et al. Effects of green tea extract supplementation and endurance training on irisin, pro-inflammatory cytokines, and adiponectin concentrations in overweight middle-aged men. Eur J Appl Physiol. 2020;120:915-23.

Banitalebi E, Kazemi A, Faramarzi M, Nasiri S, Haghighi MM. Effects of sprint interval or combined aerobic and resistance training on myokines in overweight women with type 2 diabetes: A randomized controlled trial. Life Sci. 2019;217:101-9.

Blizzard LeBlanc DR, Rioux BV, Pelech C, Moffatt TL, Kimber DE, Duhamel TA, et al. Exercise-induced irisin release as a determinant of the metabolic response to exercise training in obese youth: the EXIT trial. Physiol Rep. 2017;5(23):e13539.

Bonfante ILP, Chacon-Mikahil MPT, Brunelli DT, Gáspari AF, Duft RG, Lopes WA, et al. Combined training, FNDC5/irisin levels and metabolic markers in obese men: A randomised controlled trial. Eur J Sport Sci. 2017;17:629-37.

Boström P, Wu J, Jedrychowski MP, Korde A, Ye L, Lo JC, et al. A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. Nature. 2012;481(7382):463-8.

Briken S, Rosenkranz SC, Keminer O, Patra S, Ketels G, Heesen C, et al. Effects of exercise on Irisin, BDNF and IL-6 serum levels in patients with progressive multiple sclerosis. J Neuroimmunol. 2016;299:53-8.

Brinkmann C, Weh-Gray O, Bloch W, Brixius K, Predel H-G, Kreutz T. Effects of a combined endurance/strength training program on circulating irisin levels in overweight/obese men and women with type 2 diabetes mellitus. Exp Clin Endocrinol Diabet. 2022;130(1):37-42.

Chen Z-P, Stephens TJ, Murthy S, Canny BJ, Hargreaves M, Witters LA, et al. Effect of exercise intensity on skeletal muscle AMPK signaling in humans. Diabetes. 2003;52:2205-12.

Choi Y-K, Kim M-K, Bae KH, Seo H-A, Jeong J-Y, Lee W-K, et al. Serum irisin levels in new-onset type 2 diabetes. Diabetes Res Clin Pract. 2013;100:96-101.

Cosio PL, Crespo-Posadas M, Velarde-Sotres Á, Pelaez M. Effect of chronic resistance training on circulating irisin: systematic review and meta-analysis of randomized controlled trials. Int J Environ Res Public Health. 2021;18(5):2476.

Das UN. Metabolic syndrome pathophysiology: the role of essential fatty acids. New York: Wiley-Blackwell, 2010.

Daskalopoulou SS, Cooke AB, Gomez Y-H, Mutter AF, Filippaios A, Mesfum ET, et al. Plasma irisin levels progressively increase in response to increasing exercise workloads in young, healthy, active subjects. Eur J Endocrinol. 2014;171:343-52.

Dianatinasab A, Koroni R, Bahramian M, Bagheri-Hosseinabadi Z, Vaismoradi M, Fararouei M, et al. The effects of aerobic, resistance, and combined exercises on the plasma irisin levels, HOMA-IR, and lipid profiles in women with metabolic syndrome: A randomized controlled trial. J Exerc Sci Fitness. 2020;18:168-76.

Dünnwald T, Melmer A, Gatterer H, Salzmann K, Ebenbichler C, Burtscher M, et al. Supervised short-term high-intensity training on plasma irisin concentrations in type 2 diabetic patients. Int J Sports Med. 2019; 40:158-64.

Dundar A, Kocahan S, Sahin L. Associations of apelin, leptin, irisin, ghrelin, insulin, glucose levels, and lipid parameters with physical activity during eight weeks of regular exercise training. Arch Physiol Biochem. 2021;127:291-5.

Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629-34.

Elizondo-Montemayor L, Mendoza-Lara G, Gutierrez-DelBosque G, Peschard-Franco M, Nieblas B, Garcia-Rivas G. Relationship of circulating irisin with body composition, physical activity, and cardiovascular and metabolic disorders in the pediatric population. Int J Mol Sci. 2018;19(12):3727.

Enteshary M, Esfarjani F, Reisi J. Comparison of the effects of two different intensities of combined training on irisin, betatrophin, and insulin levels in women with type 2 diabetes. Asian J Sports Med. 2019;10(2): e68943.

Eriksson J, Taimela S, Eriksson K, Parviainen S, Peltonen J, Kujala U. Resistance training the treatment of non-insulin-dependent diabetes mellitus. Int J Sports Med. 1997;18:242-6.

Firth J, Solmi M, Wootton RE, Vancampfort D, Schuch FB, Hoare E, et al. A meta-review of "lifestyle psychiatry": the role of exercise, smoking, diet and sleep in the prevention and treatment of mental disorders. World Psychiatry. 2020;19:360-80.

Fox J, Rioux B, Goulet E, Johanssen N, Swift D, Bouchard D, et al. Effect of an acute exercise bout on immediate post-exercise irisin concentration in adults: a meta-analysis. Scand J Med Sci Sports. 2018;28(1):16-28.

Fritzen AM, Lundsgaard A-M, Kiens B. Tuning fatty acid oxidation in skeletal muscle with dietary fat and exercise. Nat Rev Endocrinol. 2020;16:683-96.

Ghanbari-Niaki A, Saeidi A, Ahmadian M, Gharahcholo L, Naghavi N, Fazelzadeh M, et al. The combination of exercise training and Zataria multiflora supplementation increase serum irisin levels in postmenopausal women. Integr Med Res. 2018;7(1):44-52.

Haas B, Schlinkert P, Mayer P, Eckstein N. Targeting adipose tissue. Diabetol Metabol Syndr. 2012;4(1):43.

Hargreaves M, McKenna MJ, Jenkins DG, Warmington SA, Li JL, Snow RJ, et al. Muscle metabolites and performance during high-intensity, intermittent exercise. J Appl Physiol. 1998;84:1687-91.

Hecksteden A, Wegmann M, Steffen A, Kraushaar J, Morsch A, Ruppenthal S, et al. Irisin and exercise training in humans–results from a randomized controlled training trial. BMC Med. 2013;11(1):235.

Higgins J. Cochrane handbook for systematic reviews of interventions. Version 5.1. 0 [updated March 2011]. The Cochrane Collaboration, 2011. www.cochrane-handbook.org.

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557-60.

Hosseini SRA, Fathi M, Ziaaldini MM, Hejazi K. The effect of eight weeks of aerobic exercise with moderate and high intensities on serum irisin and PGC-1α protein levels in obese male Wistar rats. J Shahrekord Univ Med Sci. 2021;23(1):14-9.

Huh JY, Panagiotou G, Mougios V, Brinkoetter M, Vamvini MT, Schneider BE, et al. FNDC5 and irisin in humans: I. Predictors of circulating concentrations in serum and plasma and II. mRNA expression and circulating concentrations in response to weight loss and exercise. Metabolism. 2012;61:1725-38.

Jäger S, Handschin C, Pierre JS, Spiegelman BM. AMP-activated protein kinase (AMPK) action in skeletal muscle via direct phosphorylation of PGC-1α. Proc Natl Acad Sci U S A. 2007;104:12017-22.

Jafari M, Abbasi I, Fathi Aralloo S. The effect of eight weeks high-intensity interval training (hit) on of irisin levels in obese young men. Thrita. 2020;8(2):e99505.

Jaffari H, Abedi B, Fatolahi H. The effect of 8 weeks of carob supplementation and resistance training on lipid profile and irisin in obese men. Int J Sport Exerc Health Res. 2020;4:91-5.

Jandova T, Buendía-Romero A, Polanska H, Hola V, Rihova M, Vetrovsky T, et al. Long-term effect of exercise on irisin blood levels-systematic review and meta-analysis. Healthcare (Basel). 2021;9(11):1438.

Jodeiri Farshbaf M, Alviña K. Multiple roles in neuroprotection for the exercise derived myokine Irisin. Front Aging Neurosci. 2021;13:167.

Kim H-J, Lee H-J, So B, Son JS, Yoon D, Song W. Effect of aerobic training and resistance training on circulating irisin level and their association with change of body composition in overweight/obese adults: a pilot study. Physiol Res. 2016;65:271-9.

Knutti D, Kressler D, Kralli A. Regulation of the transcriptional coactivator PGC-1 via MAPK-sensitive interaction with a repressor. Proc Natl Acad Sci U S A. 2001;98:9713-8.

Korkmaz A, Venojärvi M, Wasenius N, Manderoos S, Deruisseau KC, Gidlund E-K, et al. Plasma irisin is increased following 12 weeks of Nordic walking and associates with glucose homoeostasis in overweight/obese men with impaired glucose regulation. Eur J Sport Sci. 2019;19:258-66.

Kraemer R, Shockett P, Webb N, Shah U, Castracane V. A transient elevated irisin blood concentration in response to prolonged, moderate aerobic exercise in young men and women. Horm Metab Res. 2014;46:150-4.

Kumar AS, Maiya AG, Shastry B, Vaishali K, Ravishankar N, Hazari A, et al. Exercise and insulin resistance in type 2 diabetes mellitus: A systematic review and meta-analysis. Ann Phys Rehabil Med. 2019;62:98-103.

Lapa C, Arias-Loza P, Hayakawa N, Wakabayashi H, Werner RA, Chen X, et al. Whitening and impaired glucose utilization of brown adipose tissue in a rat model of type 2 diabetes mellitus. Sci Rep. 2017;7:16795.

Lecker SH, Zavin A, Cao P, Arena R, Allsup K, Daniels KM, et al. Expression of the irisin precursor FNDC5 in skeletal muscle correlates with aerobic exercise performance in patients with heart failure. Circ Heart Fail. 2012;5:812-8.

Micielska K, Gmiat A, Zychowska M, Kozlowska M, Walentukiewicz A, Lysak-Radomska A, et al. The beneficial effects of 15 units of high-intensity circuit training in women is modified by age, baseline insulin resistance and physical capacity. Diabetes Res Clin Pract. 2019;152:156-65.

Miyamoto-Mikami E, Sato K, Kurihara T, Hasegawa N, Fujie S, Fujita S, et al. Endurance training-induced increase in circulating irisin levels is associated with reduction of abdominal visceral fat in middle-aged and older adults. PloS One. 2015;10(3):e0120354.

Mohammad Rahimi GR, Niyazi A, Alaee S. The effect of exercise training on osteocalcin, adipocytokines, and insulin resistance: a systematic review and meta-analysis of randomized controlled trials. Osteoporos Int. 2021;32:213-24.

Motahari Rad M, Bijeh N, Attarzadeh Hosseini SR, Raouf Saeb A. The effect of two concurrent exercise modalities on serum concentrations of FGF21, irisin, follistatin, and myostatin in men with type 2 diabetes mellitus. Arch Physiol Biochem. 2020;epub ahead of print.

Motahari Rad M, Bijeh N, AttarzadehHosseini SR, RaoufSaeb A. The impact of different modes of exercise training on irisin: a systematic review and meta-analysis research. J Adv Med Biomed Res. 2021;29:125-38.

Murawska-Cialowicz E, Wolanski P, Zuwala-Jagiello J, Feito Y, Petr M, Kokstejn J, et al. Effect of HIIT with Tabata protocol on serum irisin, physical performance, and body composition in men. Int J Environ Res Public Health. 2020;17(10):3589.

Nazari Y, Nikbakht M, Habibi A. An investigation into irisin levels: acute and chronic effects of combined training and its association with anthropometric variables in overweight men. J Chem Health Risks. 2017; 7:171-9.

Norheim F, Langleite TM, Hjorth M, Holen T, Kielland A, Stadheim HK, et al. The effects of acute and chronic exercise on PGC-1α, irisin and browning of subcutaneous adipose tissue in humans. FEBS J. 2014; 281:739-49.

Nygaard H, Slettaløkken G, Vegge G, Hollan I, Whist JE, Strand T, et al. Irisin in blood increases transiently after single sessions of intense endurance exercise and heavy strength training. PLoS One. 2015;10(3): e0121367.

Oelmann S, Nauck M, Völzke H, Bahls M, Friedrich N. Circulating irisin concentrations are associated with a favourable lipid profile in the general population. PLoS One. 2016;11(4):e0154319.

Otero-Díaz B, Rodríguez-Flores M, Sánchez-Muñoz V, Monraz-Preciado F, Ordoñez-Ortega S, Becerril-Elias V, et al. Exercise induces white adipose tissue browning across the weight spectrum in humans. Front Physiol. 2018;9:1781.

Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Syst Rev. 2021;10(1):89.

Pekkala S, Wiklund PK, Hulmi JJ, Ahtiainen JP, Horttanainen M, Pöllänen E, et al. Are skeletal muscle FNDC5 gene expression and irisin release regulated by exercise and related to health? J Physiol. 2013;591: 5393-400.

Poutafkand F, Marefati H, Taherichadorneshin H. A comparison of the effects of resistance and endurance training protocols on serum irisin level and alkaline phosphatase activity in sedentary obese women. Pol J Sport Tourism. 2020;27(4):23-8.

Qiu S, Cai X, Sun Z, Schumann U, Zuegel M, Steinacker JM. Chronic exercise training and circulating irisin in adults: A meta-analysis. Sports Med. 2015;45:1577-88.

Rashid FA, Abbas HJ, Naser NA, Ali A. Effect of long-term moderate physical exercise on irisin between normal weight and obese men. ScientificWorldJournal. 2020;2020:1897027.

Rezaeimanesh D. Effects of Interval Training on Irisin and Insulin Resistance in Overweight Men. Archives of Pharmacy Practice. 2020;1:78.

Roca-Rivada A, Castelao C, Senin LL, Landrove MO, Baltar J, Crujeiras AB, et al. FNDC5/irisin is not only a myokine but also an adipokine. PloS One. 2013;8(4): e60563.

Safarimosavi S, Mohebbi H, Rohani H. High-intensity interval vs. continuous endurance training: Preventive effects on hormonal changes and physiological adaptations in prediabetes patients. J Strength Cond Res. 2021;35:731-8.

Sanayei M, Hajizadeh-Sharafabad F, Amirsasan R, Barzegar A. High intensity interval training with or without Chlorella vulgaris supplementation in obese and overweight women: effects on mitochondrial biogenesis, performance, and body composition. Br J Nutr. 2021;epub ahead of print.

Sari-Sarraf V, Nikoukheslat S, Niknam Z. Effect of 8 weeks exercise on irisin in obese women. J Woman's Reproduct Health. 2017;2(1):1-9.

Scharhag-Rosenberger F, Meyer T, Wegmann M, Ruppenthal S, Kaestner L, Morsch A, et al. Irisin does not mediate resistance training-induced alterations in resting metabolic rate. Med Sci Sports Exerc. 2014;46: 1736-43.

Smart NA, Waldron M, Ismail H, Giallauria F, Vigorito C, Cornelissen V, et al. Validation of a new tool for the assessment of study quality and reporting in exercise training studies: TESTEX. Int J Evid Based Healthc. 2015;13(1):9-18.

Suwa M, Nakano H, Radak Z, Kumagai S. Endurance exercise increases the SIRT1 and peroxisome proliferator-activated receptor γ coactivator-1α protein expressions in rat skeletal muscle. Metabolism. 2008;57:986-98.

Tofighi A, Alizadeh R, Tolouei Azar J. The effect of eight weeks high intensity interval training (HIIT) on serum amounts of FGF21 and irisin in sedentary obese women. Stud Med Sci. 2017;28:453-66.

Tsuchiya Y, Ando D, Goto K, Kiuchi M, Yamakita M, Koyama K. High-intensity exercise causes greater irisin response compared with low-intensity exercise under similar energy consumption. Tohoku J Exp Med. 2014; 233:135-40.

Tsuchiya Y, Ando D, Takamatsu K, Goto K. Resistance exercise induces a greater irisin response than endurance exercise. Metabolism. 2015;64:1042-50.

Verduci E, Calcaterra V, Di Profio E, Fiore G, Rey F, Magenes VC, et al. Brown adipose tissue: new challenges for prevention of childhood obesity. a narrative review. Nutrients. 2021;13(5):1450.

Vliora M, Grillo E, Corsini M, Ravelli C, Nintou E, Karligiotou E, et al. Irisin regulates thermogenesis and lipolysis in 3T3-L1 adipocytes. Biochim Biophys Acta Gen Subj. 2022;1866(4):130085.

Winn NC, Grunewald ZI, Liu Y, Heden TD, Nyhoff LM, Kanaley JA. Plasma irisin modestly increases during moderate and high-intensity afternoon exercise in obese females. PloS One. 2017;12(1):e0170690.

Zhang C, Ding Z, Lv G, Li J, Zhou P, Zhang J. Lower irisin level in patients with type 2 diabetes mellitus: A case-control study and meta-analysis. J Diabetes. 2016;8(1):56-62.

Zhao J, Su Z, Qu C, Dong Y. Effects of 12 weeks resistance training on serum irisin in older male adults. Front Physiol. 2017;8:171.