Comparative Impact of Various Exercises on Circulating Irisin in Healthy Subjects: A Systematic Review and Network Meta-Analysis

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Irisin is a myokine that is secreted from skeletal muscle during exercise and increases lipid metabolism, converting white adipose tissue to brown adipose tissue. Recent studies have shown conflicting results in relation to chronic and acute exercise and irisin. The aim of this study was to evaluate the effects of chronic and acute exercise training on circulating (plasma/serum) irisin level in healthy subjects. We conducted a search of Cochrane Library, PubMed, ISI, Scopus, Embase, and Pedro up to September 2021. A random effects network meta-analysis was performed to calculate the pooled estimate of standardized mean difference (SMD) for acute and chronic exercise effects on irisin level, using Hedge’s g statistic. Of the 16 studies included, six were acute exercise studies (175 participants). The aerobic (Hedge’s g = 0.23; 95% CI: -0.58, 1.03) and the anaerobic exercises (Hedge’s g = 0.12; 95% CI: -0.45, 0.70) were associated with the increased level of irisin, compared to the control. In the ten chronic exercise studies (433 participants), the resistance training was superior to anaerobic and aerobic training (P score = 0.632). However, comparing acute and chronic exercise studies, acute training showed the most excellent potential as the best treatment to improve the irisin level (P score = 0.721). This network meta-analysis showed that acute aerobic exercise has a more effect on irisin levels than acute anaerobic exercise. Also, chronic resistance training has the greatest additive effect on irisin levels compared to chronic aerobic and anaerobic training.

1. Introduction

Regular exercise plays a vital role in preventing chronic diseases. However, the molecular mechanisms induced by exercise training that led to health outcomes are not fully understood. In 2012, Bostrom et al. reported that exercise increased expression of the peroxisome proliferator-activated receptor-gamma coactivator 1-alpha (PGC-1α) and induced FNDC5 in skeletal muscle, which breaks down to irisin and is released into the bloodstream. Irisin increases the expression of UCP1 in white adipose tissue (WAT) and turns WAT into brown adipose tissue (BAT), which leads to the induction of thermogenesis, improved lipid metabolism, glucose homeostasis, and weight loss. In general, irisin secretion can demonstrate the health benefits of exercise and be suggested as a therapeutic target for obesity and type 2 diabetes [1].

While contradictory results have been reported regarding the effect of chronic exercise on circulating (plasma/serum) irisin in adults [1–5], a study by Bostrom et al. reported that ten weeks of aerobic exercise with 65% of maximal oxygen consumption (VO2max) were associated with a twofold increase in circulating irisin compared with the untrained adult. But in another research, data showed that the irisin in trained people decreased significantly compared to inactive people [6]. Evidence from another study showed that neither endurance training (aerobic exercise) nor resistance training could increase circulating irisin levels
2.1. Data Sources and Search Strategies. MANMA for our study. Reviews and Meta-Analyses Network Meta-Analyses (PRISMA) for the PubMed search, and the same search strategy was also performed for other databases (see electronic supplementary material Appendix S1). In addition, the reference lists of previous meta-analysis articles were manually searched to ensure that no relevant articles had been missed.

2.2. Inclusion and Exclusion Criteria. Duplicate records were removed using Endnote software. Then, the two researchers (F.K and E.S) examined the titles and abstracts of the studies independently. Studies that met the inclusion criteria were detected and reviewed by the same authors independently. Disputes were resolved by discussion or consultation with a third author if necessary. The details of the inclusion criteria were as follows: (1) the study design should be an RCT. (2) Participants must be healthy. (3) The type of exercise interventions can include aerobic, anaerobic, or resistance training. (4) Chronic exercise included at least eight weeks of exercise. (5) Studies have a control group. (6) The primary outcome is circulating (plasma/serum) irisin levels. (7) Irisin was measured with an ELISA kit. The details of the exclusion criteria were as follows: (1) participants must not be more than 60 years old. (2) Animal studies were omitted. (3) Participant with metabolic diseases, including obesity or diabetes, was excluded. (4) The NRs studies were omitted. (5) Review, meta-analysis, cross-sectional, and crossover studies were excluded. (6) The posters were removed because they had limited information. (7) Crossover studies were omitted.

2.3. Data Extraction. Two researchers (F.K and E.S) extracted the data independently. Studies characteristics (study population, sample size, gender, age, and body mass index (BMI)), exercise training variables (kind of exercise, intensity, total time, number of sessions, and duration of each session), and outcome variables (mean or pretest and posttest for the level of irisin) were extracted.

2.4. Risk of Bias Assessment. Two researchers (F.K and E.S) examined the methodological quality of each study independently based on the Cochrane Collaboration “Risk of Bias 2” Tool, which was initially designed for assessing the quality of RCTs [19]. The quality domains were randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Each study was therefore identified to be as low, moderate, or high risk of bias.

2.5. Statistical Analyses. The netmeta package in the R software version 4.1.2 (The R Foundation for Statistical Computing, Vienna, Austria) was applied to perform network meta-analysis by combining the direct and indirect effects of various interventions. The Cochran’s Q and I-square ($I^2$) statistics were calculated to evaluate the inconsistency and heterogeneity across studies. The $I^2$ statistic of 25%, 50%, or 75% indicates low, moderate, or high heterogeneity. A random effects network meta-analysis was used to calculate pooled estimates of standardized mean difference (SMD) using Hedge’s g statistic with 95% confidence intervals (95% CI). Random effects model was used since there was
considerable amount of heterogeneity between the studies ($I^2 > 50\%$). Besides, it has been recommended that random effects models be employed in meta-analysis in preference to fixed effects models [20]. The network structure was graphically displayed through the network plot. Pairwise comparison of the interventions was presented in the league table using standardized mean difference (SMD, 95% confidence interval). All treatments were ranked by $P$ score to calculate the amount of certainty that a single treatment is better than another competing treatment. The $P$ score ranges from 0 to 1, with higher scores representing a better treatment. Potential publication bias was visually investigated using funnel plot along with a modified Egger’s method by Thompson and Sharp [21]. Meta regression was also applied to assess whether duration of exercise could potentially affect the irisin level.

### 3. Results

#### 3.1. Description of Included Studies

A total of 277 records were identified after removing duplicates. Of these records, 50 were considered potentially relevant after the preliminary screening of article titles and abstracts. Finally, after applying the inclusion and exclusion criteria, a total of 16 articles were selected for network meta-analysis (Figure 1). The agreement rate for study selection and data extraction between the two researchers were 89.1% and 93%, respectively. In the included articles, 10 studies (433 participants) examined the effects of chronic exercise, six studies (175 participants) examined the effects of acute exercise, three studies (83 participants) examined the effects of acute anaerobic training, three studies (92 participants) examined the effects of acute aerobic training, six studies (205 participants) surveyed the impact of chronic aerobic training, five studies (212 participants) investigated the effects of chronic resistance training, and one study (16 participants) examined the effects of chronic anaerobic training. A total of 608 participants, including 360 men and 248 women, were entered in this review. The overall mean age of exercised groups and control groups were $28.9 \pm 3.27$ and $29.21 \pm 3.63$ years, respectively. Detailed study characteristics and the list of included studies are reported in Table 1.

#### 3.2. Network Meta-Analysis (NMA)

We implemented three different strategies for aggregating the studies (Figure 2). First, an NMA of irisin level was conducted based on acute training interventions, including three aerobic training studies (83 participants) and three anaerobic training studies (92 participants). The total heterogeneity was not significant among the studies ($\tau^2 = 0.180$, $I^2 = 51.1\%$, $Q_{total} = 8.18$; $P = 0.085$). In the direct comparisons, the acute aerobic (Hedge’s $g = 0.23$; 95% CI: -0.58, 1.03) and the acute anaerobic (Hedge’s $g = 0.12$; 95% CI: -0.45, 0.70) were associated with the increased level of irisin, compared with control. Based on the $P$ score ranking, the acute aerobic training was superior to the acute anaerobic training and control group ($P$ score = 0.644) (Figure 3). However, the league table
Table 1: Characteristics of the studies included in the network meta-analysis.

| Study (year)         | Population                  | Exercised group: age (years) | Control group: age (years) | Exercised group: BMI | Control group: BMI | Sex (M/F) | Description of exercise training intervention and control | Blood sample | Blood sampling time |
|----------------------|-----------------------------|-----------------------------|---------------------------|---------------------|-------------------|-----------|-----------------------------------------------------------|--------------|---------------------|
| Algul et al. (2017)  | Healthy young men           | 19.2 ± 0.7                  | 19.5 ± 0.6                | 21.3 ± 0.4          | 21.7 ± 0.4        | 60 M      | K: aerobic exercise, acute I: 64-76% MHR (moderate-intensity) T: 30 min N: one session | Serum        | Before and immediately after exercise |
| Dundar et al. (2021) | Healthy adolescent boys     | 13-16                       | 13-16                     | 23.75 ± 1.75        | 24.85 ± 1.6       | 34 M      | K: aerobic exercise, chronic I: (basketball training) no mention T: 120 min N: 5 sessions/week D: 8 weeks | Serum        | Before and after the eight-week exercise program |
| Fernandez-del-Valle et al. (2018) | Healthy young adult         | Males: 21.18 ± 1.93 | Females: 21.35 ± 2.52     | 22.11 ± 1.68        | 23.04 ± 1.94      | 14 M/12 F | K: resistance exercise, chronic I: 70-80% 1RM (high-intensity) T: 55 min N: 3 sessions/week D: 3 weeks | Serum        | Before and after the exercise |
| Hecksteden et al. (2013)A | Healthy men and women       | 49 ± 7                      | 50 ± 7                    | 23.5 ± 3.5          | 24.5 ± 3.1        | 21 M/62 F | K: aerobic exercise, chronic I: 60% heart rate reserve T: 45 min N: 3 sessions/week D: 26 weeks | Serum        | Before the training period and at 2 to 7 days after the final training bout |
| Hecksteden et al. (2013)B | Healthy men and women       | 48 ± 7                      | 50 ± 7                    | 24.9 ± 3.4          | 24.5 ± 3.1        | 30 M/49 F | K: resistance exercise, chronic I: two sets of 15 repetitions with 100% of the 20-repetition maximum (high-intensity) N: 3 sessions/week D: 26 weeks | Serum        | Before the training period and at 2 to 7 days after the final training bout |
| Izaddoust and Shabani (2017) | Untrained women            | 24.6 ± 2.45                 | 26.44 ± 4.18              | 23.45 ± 2.83        | 23.28 ± 2.62      | 16 F      | K: resistance exercise, chronic I: 65-75% 1RM T: 65 min N: 3 sessions/week D: 8 weeks | Serum        | Before and 24 hours after the last training session |
| Kabak et al. (2018)   | Professional kick-boxers    | 20.20 ± 1.62                | 20.00 ± 1.33              | 23.47 ± 2.94        | 24.14 ± 2.66      | 30 M      | K: anaerobic exercise, acute I: HIIT T: four 30-s Wingate anaerobic test N: one session | Plasma       | Before and after exercise (within 1 min) |
| Healthy young        | 21 ± 1                      | 21 ± 1                      | 21.9 ± 1.7                | 23.1 ± 3.4          | 16 M/9 F         | K: aerobic exercise, chronic | Serum        | Before and after exercise |

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| Study (year)                        | Population                  | Exercised group: age (years) | Control group: age (years) | Exercised group: BMI | Control group: BMI | Sex (M/F) | Description of exercise training intervention and control | Blood sample | Blood sampling time                        |
|-----------------------------------|-----------------------------|------------------------------|----------------------------|---------------------|-------------------|------------|------------------------------------------------------------|--------------|--------------------------------------------|
| Miyamoto-Mikami et al. (2015) [26]| women and men               |                              |                            |                     |                   |            | I: 60-70% vo2max                                          | Serum        | After the 8-week training                  |
|                                   |                             |                              |                            |                     |                   |            | T: 55 min                                                 |              |                                            |
|                                   |                             |                              |                            |                     |                   |            | N: 3 sessions/week                                        |              |                                            |
|                                   |                             |                              |                            |                     |                   |            | D: 8 weeks                                                |              |                                            |
| Murawska-Cialowicz et al. (2020)  | Healthy men                 | 32.39 ± 6.63                 | 25.35 ± 3.28               | 25.75 ± 2.94        | 24.16 ± 2.19      | 25 M       | K: aerobic exercise, chronic                              | Serum        | Before and after the 8-week training        |
|                                   |                             |                              |                            |                     |                   |            | I: HIIT                                                   |              |                                            |
|                                   |                             |                              |                            |                     |                   |            | T: 60 min                                                 |              |                                            |
|                                   |                             |                              |                            |                     |                   |            | N: 2 sessions/week                                        |              |                                            |
|                                   |                             |                              |                            |                     |                   |            | D: 8 weeks                                                |              |                                            |
| Nicolini et al. (2020) [28]       | Healthy young men           | 23 ± 3                       | 25 ± 4                     | No mention          | No mention        | 40 M       | K: anaerobic running, acute                              | Serum        | Before and after exercise                  |
|                                   |                             |                              |                            |                     |                   |            | I: high-intensity interval exercise                       |              |                                            |
|                                   |                             |                              |                            |                     |                   |            | T: 17.5 min                                               |              |                                            |
|                                   |                             |                              |                            |                     |                   |            | N: one session                                            |              |                                            |
| Qiu et al. (2018) [29]            | Healthy adults              | 22.0 ± 1.1                   | 22.2 ± 1.9                 | 22.0 ± 1.1          | 22.2 ± 1.9        | 16 M       | K: aerobic running, acute                                | Serum        | Before and after exercise                  |
|                                   |                             |                              |                            |                     |                   |            | I: 80% vo2max (high-intensity)                            |              |                                            |
|                                   |                             |                              |                            |                     |                   |            | T: 60 min                                                 |              |                                            |
|                                   |                             |                              |                            |                     |                   |            | N: one session                                            |              |                                            |
| Rodziewicz et al. (2020) [30]     | Master endurance master athletes | 58.6 ± 4.3                  | 57.4 ± 2.9                 | 24.2 ± 0.5          | 24.0 ± 0.4        | 22 M       | K: anaerobic running, acute                              | Plasma       | Before and after exercise                  |
|                                   |                             |                              |                            |                     |                   |            | I: high-intensity interval exercise                       |              |                                            |
|                                   |                             |                              |                            |                     |                   |            | T: exercise test until exhaustion                         |              |                                            |
|                                   |                             |                              |                            |                     |                   |            | N: one session                                            |              |                                            |
| Rostami et al. (2019) [31]        | Healthy young untrained women | 24.66 ± 2.29                 | 26.44 ± 4.18               | 26.7 ± 2.7          | 23.28 ± 2.62      | 20 F       | K: aerobic exercise, chronic                              | Serum        | 48 h before and after the last training session |
|                                   |                             |                              |                            |                     |                   |            | I: 65-75%MHR (moderate-intensity)                         |              |                                            |
|                                   |                             |                              |                            |                     |                   |            | T: 65 min                                                 |              |                                            |
|                                   |                             |                              |                            |                     |                   |            | N: 3 sessions/week                                        |              |                                            |
|                                   |                             |                              |                            |                     |                   |            | D: 8 weeks                                                |              |                                            |
| Scharhag-Rosenberger et al. (2014) | Healthy men and women        | 47 ± 7                       | 50 ± 7                     | 25 ± 3.4            | 24.2 ± 3.2        | 29 M/45 F  | K: resistance exercise, chronic                           | Serum        | Before and after exercise                  |
|                                   |                             |                              |                            |                     |                   |            | I: 16–20 repetitions at 64%–71% 1RM                       |              |                                            |
|                                   |                             |                              |                            |                     |                   |            | T: 65 min                                                 |              |                                            |
|                                   |                             |                              |                            |                     |                   |            | N: 3 sessions/week                                        |              |                                            |
|                                   |                             |                              |                            |                     |                   |            | D: 24 weeks                                               |              |                                            |
| Kraemer et al. (2014) [12]        | Healthy men                 | 22.71 ± 1.6                  | 22.71 ± 1.6                | 24.29 ± 2.94        | 24.29 ± 2.94      | 7 M        | K: aerobic exercise, acute                                | Plasma       | Before and after exercise                  |
|                                   |                             |                              |                            |                     |                   |            | I: 60% of VO2max (moderate-intensity)                      |              |                                            |
|                                   |                             |                              |                            |                     |                   |            | T: 90 min                                                 |              |                                            |
|                                   |                             |                              |                            |                     |                   |            | N: one session                                            |              |                                            |
| Shabani and Izaddoust (2018) [32]  | Healthy untrained women      | 24.66 ± 2.29                 | 25.50 ± 4.80               | 26.70 ± 2.70        | 23.28 ± 2.62      | 18 F       | K: aerobic exercise, chronic                              | Serum        | Before and after exercise                  |
|                                   |                             |                              |                            |                     |                   |            | I: 60–75% MHR                                             |              |                                            |
|                                   |                             |                              |                            |                     |                   |            | T: 65 min                                                 |              |                                            |
Control distance (Hedge) was associated with decreased and the chronic anaerobic (Hedge) was superior to chronic aerobic with increased level of irisin, compared with control. Also, the league table showed no significant difference between aerobic training and anaerobic training (Hedge’s $g = 0.10$; 95% CI: -0.89, 1.09) (Table 2).

In the second strategy, we implemented the NMA based on the division of chronic interventions into three groups, including aerobic training (205 participants), anaerobic training (16 participants), and resistance training (212 participants). The total heterogeneity was reported high ($\tau^2 = 0.322$, $I^2 = 71.3\%$, $Q_{total} = 31.34$; $P < 0.001$). The chronic aerobic (Hedge’s $g = -0.18$; 95% CI: -0.73, 0.37) was associated with decreased and the chronic anaerobic (Hedge’s $g = 0.16$; 95% CI: -1.12, 1.43) and the chronic resistance (Hedge’s $g = 0.12$; 95% CI: -0.47, 0.71) were associated with increased level of irisin, compared with control. Also, the chronic resistance was superior to chronic anaerobic and chronic aerobic ($P$ score = 0.632) (Figure 3). However, the league table showed no significant difference between any pair of training interventions (Table 2).

Finally, we implemented an NMA based on aggregating all acute and chronic studies. The total heterogeneity was estimated at ($\tau^2 = 0.221$, $I^2 = 63.1\%$) and suggested that there was statistically significant heterogeneity ($Q_{total} = 43.42$; $P < 0.001$). Compared to the control, the acute interventions had a better effect on irisin level improvement with Hedge’s $g$ of 0.15 (95% CI: -0.35, 0.65). Still, no statistically significant. The chronic training was also associated with a nonsignificant decrease in the level of irisin (Hedge’s $g = -0.03$; 95% CI: -0.37, 0.31). The acute training showed the greatest potential as the best treatment to improve the irisin level ($P$ score = 0.721) (Figure 3). However, there was no evidence for a statistically difference between the acute and chronic trainings (Hedge’s $g = 0.18$; 95% CI: -0.42, 0.78) (Table 2).

### 3.3. Publication Bias Analysis

The funnel plot and the modified Egger’s regression model (bias coefficient = −0.273, $P = 0.860$) showed no evidence of potential publication bias (Figure 4).

### 3.4. Meta Regression

The result of meta regression revealed no significant effect of exercise duration on irisin level (Table 3).
3.5. Risk of Bias. Risk of bias table and summary plot were presented in Figures 5 and 6.

4. Discussion

4.1. Summary of the Main Results. The level of circulating irisin after acute aerobic and acute anaerobic exercise was higher than the control group, but no significant difference was observed between aerobic training and anaerobic training. Chronic resistance training and chronic anaerobic exercise had a moderate effect on increasing circulating irisin, but chronic aerobic exercise decreased irisin levels compared to the control group. In addition, acute exercise had a better impact on the level of irisin, but it was not significant. Also, irisin level after chronic training had a nonsignificant decrease vs. the control group. Overall, there was no significant difference between acute and chronic intervention on circulating irisin.

4.2. Interpretation. The impact of different forms of exercise training on plasma irisin is not clear. It is likely that chronic resistance training might be associated with an increased
circulating irisin levels. First, Bostrom et al. (2012) showed that irisin increased after 10-week training healthy overweight adults [1]. Other studies have reported that circulating irisin levels increase after chronic resistance training [34, 35]. The results of the present study are consistent with the data of the Bostrom study. Second, increased muscle mass following chronic resistance training is associated with increased FNDC5 expression, and researchers in one study found that irisin was associated with muscle mass [15]. Scharhag-Rosenberger et al. showed that strength training did not change irisin levels [13]. They reported that the possible cause was the storage time of blood samples in the freezer. Serum storage in the freezer for a long time will degrade irisin, and erroneous data may be obtained.

Chronic anaerobic exercise is also associated with increased irisin levels. Huh et al. demonstrated that serum irisin correlated with exercise intensity [11]. Increased irisin may be stimulated by metabolic acidosis and the anaerobic system. For this reason, irisin has increased after chronic anaerobic exercise; however, it was not statistically significant.

On the other hand, chronic aerobic exercise has reduced plasma irisin. First, recent studies have shown that irisin is not only a myokine released from skeletal muscle but also released from adipose tissue and is known as an adipokine [36, 37]. Irisin decreases after weight loss due to surgery [15]. Given that chronic aerobic exercise is associated with weight loss [38] and body fat loss [39], it is likely that irisin in circulation after chronic aerobic exercise is reduced due to weight loss and reduce adipose tissue. Also, irisin levels also seem to be positively correlated with biceps circumference as an indicator of muscle mass [15]. Second, cross-sectional studies have also reported that irisin has a positive association with insulin resistance (IR) [40, 41] and fasting blood glucose [40, 42] in nondiabetic participants. As a result, irisin may be involved in regulating glucose homeostasis [42]. Probably, the reason for the decrease in irisin in people who have exercised chronic aerobic training is the regulation of blood glucose. Because, chronic aerobic exercise improves insulin sensitivity and decreases IR [43]. Third, recent evidence suggests that circulating irisin levels are correlated with BMI, and reduction in BMI in the trained group is associated with a decrease in irisin [15]. Fourth, irisin level reduction is associated with the pattern of decrease in the levels of lipid as a result of chronic aerobic exercise [5]. On the other hand, several studies have reported that plasma irisin increased after chronic aerobic exercise, which is consistent with the results of the study of Bostrom et al. [26, 27].

In addition, acute aerobic exercise has increased circulating irisin. Recent studies have shown that irisin increases energy intake and oxidative metabolism [44, 45]. There are conflicting results regarding exercise and energy balance, with some studies reporting that acute exercise has no effect on energy intake [46, 47]. It is noteworthy that the duration and intensity of physical activity have a significant effect on plasma irisin. As a result, future studies are needed to investigate the impact of different training protocols on energy-regulating hormones, including irisin. Also, several studies [1, 4, 9, 10] have revealed that FNDC5 mRNA levels in skeletal muscle reach their peak a one hour after an acute session of endurance exercise and return to the baseline level after 24 h [10]. Peak concentrations of irisin occurred at 0 h or 1 h after training, and that the increase is transient [4, 10–12]. As a result, the half-life of irisin in humans is less than an hour [48]. This is probably why irisin increases after

| Variable                | Coefficient (S.E) | 95% CI         | I²    | Pvalue |
|-------------------------|-------------------|----------------|-------|--------|
| Duration of exercise    | Acute             | -0.005 (0.010) | -0.037, 0.026 | 56.5%  | 0.631  |
|                         | Chronic           | -0.009 (0.021) | -0.056, 0.037 | 70%    | 0.655  |

Figure 4: Funnel plot for evaluating the publication bias (no potential asymmetry was observed).

Table 3: Meta regression model for evaluating the effect of exercise duration on irisin level (pooled Hedges SMD as the response variable).
acute aerobic exercise and decreases after chronic aerobic exercise. Irisin levels are usually measured immediately after an acute training, but will be calculated after chronic exercise 12 to 24 hours after the last workout. So, the short half-life of irisin can be one of the main reasons for the variation in circulating irisin levels after different exercises.

In addition, day-night rhythm affects irisin secretion. So, it has the lowest levels at 6:00 in the mornings and highest levels at 9 in the evening [49]. Parameters such as age, gender, and BMI are also significantly associated with irisin. Researchers have reported that irisin levels are lower in women than in men, possibly due to lower muscle mass in women than men in average [50]. For this reason, in this study, participants with a mean age of 13 and 59 years and BMI between 21 and 27 were selected. And older people over 60 years and obese adults were excluded from the present study.

4.3. Perspective. There has been no systematic review before this one of network meta-analysis designed to evaluate the impact of various exercises on circulating irisin. Our results show that acute aerobic training and chronic resistance training increase circulating irisin level compared to acute aerobic exercise and decreases after chronic aerobic exercise.

### Figure 5: Risk of bias table.

| Study                  | D1 | D2 | D3 | D4 | D5 | Overall |
|------------------------|----|----|----|----|----|---------|
| Algul                  | ○  | ●  | ●  | ●  | ○  |         |
| Dundar                 | ○  | ●  | ●  | ●  | ●  |         |
| Fernandez-Del-Valle    | ○  | ●  | ●  | ●  | ●  |         |
| Hechsteden             | ○  | ●  | ●  | ●  | ●  |         |
| Izaddoust              | ○  | ●  | ●  | ●  | ●  |         |
| Kabak                  | ○  | ●  | ●  | ●  | ●  |         |
| Kraemer                | ○  | ●  | ●  | ●  | ●  |         |
| Miyamoto-Mikami        | ○  | ●  | ●  | ●  | ●  |         |
| Murawska-Cialowicz     | ○  | ●  | ●  | ●  | ●  |         |
| Nicolini               | ○  | ●  | ●  | ●  | ●  |         |
| Qiu                    | ○  | ●  | ●  | ●  | ●  |         |
| Rodziewicz             | ○  | ●  | ●  | ●  | ●  |         |
| Rostami                | ○  | ●  | ●  | ●  | ●  |         |
| Scharhag-Rosenberger   | ○  | ●  | ●  | ●  | ●  |         |
| Shabani                | ○  | ●  | ●  | ●  | ●  |         |
| Chireh                 | ○  | ●  | ●  | ●  | ●  |         |

Domains:
- D1: Bias arising from the randomization process.
- D2: Bias due to deviations from intended intervention.
- D3: Bias due to missing outcome data.
- D4: Bias in measurement of the outcome.
- D5: Bias in selection of the reported result.

Judgement
- High
- Some concerns
- Low

### Figure 6: Risk of bias summary plot (percentage of studies examining the impact of exercise training in healthy subjects with low risk, some concerns, and high risk of bias for each feature of the Cochrane Collaboration "Risk of Bias 2" Tool.)
anaerobic training and chronic aerobic and anaerobic, respectively. Also, our findings show that acute training had a better effect on irisin level improvement vs. chronic training. But more further studies with more diverse designs to compare the types of exercise (acute and chronic) in healthy and patients individuals should be performed in the future.

4.4. Strengths and Limitations. The present network meta-analysis has several strengths. First, the previous meta-analysis study by Qiu et al. examined three RCT studies, while the present meta-analysis evaluated 16 RCT studies with 608 subjects [8]. Second, in previous meta-analysis studies, chronic aerobic, resistance, anaerobic exercise, acute aerobic, and anaerobic training studies were not separated or compared. Third, to minimize report bias, the study methodology was registered a priori. Fourth, it is to date, the impact of chronic aerobic, resistance and acute exercise on circulating irisin have not been compared in network meta-analysis studies. Fifth, in this study, obese and diabetic individuals were excluded, and only the impact of various types of physical exercise on irisin levels in healthy individuals was investigated.

The study also has some limitations. There were few studies on the effect of acute exercise on irisin levels. Lack of studies evaluating the direct comparison of acute and chronic or aerobic and resistance interventions so that we could have a precise estimation of inconsistency between the studies. Also, a relatively small number of studies have also examined the impact of combined resistance and aerobic exercise on circulating irisin.

5. Conclusions

This network meta-analysis showed that the acute aerobic training was superior to the acute anaerobic training and control group. Also, chronic resistance training has the most significant additive effect on irisin levels than chronic aerobic and anaerobic training. This network meta-analysis also showed that study design in randomized controlled trials, type of exercise, and training intensity might be the primary sources for contradictory results reported in the literature.

Conflicts of Interest

The authors declare no conflicts of interest.

Authors’ Contributions

E.S. and A.AS conducted and accomplished the search strategies. F.K. and E.S. carried out the screenings, data extraction, and bias assessment. E.S. and A.AS performed the statistical analysis. F.K., E.S., and A.AS drafted and revised the manuscript. All authors read and approved the final manuscript.

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Supplementary Materials

Search queries: Embase, ISI, Cochrane, PubMed, and Scopus. (Supplementary Materials)

References

[1] P. Boström, J. Wu, M. P. Jedrychowski et al., “A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis,” Nature, vol. 481, no. 7382, pp. 463–468, 2012.
[2] A. Hecksteden, M. Wegmann, A. Steffen et al., “Irisin and exercise training in humans – results from a randomized controlled training trial,” BMC medicine, vol. 11, no. 1, pp. 1–8, 2013.
[3] S. Pekkala, P. K. Wiklund, J. J. Hulmi et al., “Are skeletal muscle FNDC5 gene expression and irisin release regulated by exercise and related to health?,” The Journal of physiology, vol. 591, no. 21, pp. 5393–5400, 2013.
[4] F. Norheim, T. M. Langleite, M. Hjorth et al., “The effects of acute and chronic exercise on PGC-1α, irisin and browning of subcutaneous adipose tissue in humans,” The FEBS journal, vol. 281, no. 3, pp. 739–749, 2014.
[5] A. Dundar, S. Kocahan, and L. Sahin, “Associations of apelin, leptin, irisin, ghrelin, insulin, glucose levels, and lipid parameters with physical activity during eight weeks of regular exercise training,” Archives of physiology and biochemistry, vol. 127, no. 4, pp. 291–295, 2021.
[6] M. Pardo, A. B. Crujeiras, M. Amil et al., “Association of irisin with fat mass, resting energy expenditure, and daily activity in conditions of extreme body mass index,” International journal of endocrinology, vol. 2014, Article ID 857270, 9 pages, 2014.
[7] Y. Tsuchiya, D. Ando, K. Takamatsu, and K. Goto, “Resistance exercise induces a greater irisin response than endurance exercise,” Metabolism, vol. 64, no. 9, pp. 1042–1050, 2015.
[8] S. Qiu, X. Cai, Z. Sun, U. Schumann, M. Zuegel, and J. M. Steinacker, “Chronic exercise training and circulating irisin in adults: a meta-analysis,” Sports medicine, vol. 45, no. 11, pp. 1577–1588, 2015.
[9] J. Brenmoehl, E. Albrecht, K. Komolka et al., “Irisin is elevated in skeletal muscle and serum of mice immediately after acute exercise,” International journal of biological sciences, vol. 10, no. 3, pp. 338–349, 2014.
[10] H. Nygaard, G. Slettalokken, G. Vegge et al., “Irisin in blood increases transiently after single sessions of intense endurance exercise and heavy strength training,” PloS one, vol. 10, no. 3, article e0121367, 2015.
[11] J. Y. Huh, V. Mougiou, A. Kabasakalis et al., “Exercise-induced irisin secretion is independent of age or fitness level and increased irisin may directly modulate muscle metabolism through AMPK activation,” The Journal of Clinical Endocrinology & Metabolism, vol. 99, no. 11, pp. E2154–E2161, 2014.
[12] R. Kraemer, P. Shockett, N. Webb, U. Shah, and V. J. H. Castracane, “A transient elevated irisin blood concentration in response to prolonged, moderate aerobic exercise in young men and women,” Hormone and metabolic research, vol. 46, no. 2, pp. 150–154, 2014.
[13] F. Scharhag-Rosenberger, T. Meyer, M. Wegmann et al., “Irisin does not mediate resistance training-induced alterations in resting metabolic rate,” Medicine and science in sports and exercise, vol. 46, no. 9, pp. 1736–1743, 2014.
[14] C. Moraes, V. Leal, S. Marinho et al., “Resistance exercise training does not affect plasma irisin levels of hemodialysis patients,” Hormone and Metabolic Research, vol. 45, no. 12, pp. 900–904, 2013.

[15] J. Y. Huh, G. Panagiotou, V. Mougios et al., “FND5C 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, vol. 61, no. 12, pp. 1725–1738, 2012.

[16] B. Rouse, A. Chaimani, and T. Li, “Network meta-analysis: an introduction for clinicians,” Internal and emergency medicine, vol. 12, no. 1, pp. 103–111, 2017.

[17] J. Fox, B. V. Rioux, E. D. Goulet et al., “Effect of an acute exercise bout on immediate post-exercise irisin concentration in adults: a meta-analysis,” Scandinavian journal of medicine & science in sports, vol. 28, no. 1, pp. 16–28, 2018.

[18] D. Moher, A. Liberati, J. Tetzlaff, D. G. Altman, and Prisma Group, “Reprint—preferred reporting systems for systematic reviews and meta-analyses: the PRISMA statement,” Physical therapy, vol. 89, no. 9, pp. 873–880, 2009.

[19] J. P. Higgins, J. Savovic, M. J. Page, R. G. Elbers, and J. A. Sterne, “Assessing risk of bias in a randomized trial,” in Cochrane Handbook for Systematic Reviews of Interventions, pp. 205–228, John Wiley & Sons, 2019.

[20] J. E. Hunter and F. L. Schmidt, “Fixed effects vs. random effects meta-analysis models: implications for cumulative research knowledge,” International journal of selection and assessment, vol. 8, no. 4, pp. 275–292, 2000.

[21] S. G. Thompson and S. J. Sharp, “Explaining heterogeneity in meta-analysis: a comparison of methods,” Statistics in medicine, vol. 18, no. 20, pp. 2693–2708, 1999.

[22] S. Algul, C. Ozdenk, and O. Ozcelik, “Variations in leptin, nesfatin-1 and irisin levels induced by aerobic exercise in young trained and untrained male subjects,” Biology of sport, vol. 34, no. 4, pp. 339–344, 2017.

[23] M. Fernandez-del-Valle, M. J. Short, E. Chung et al., “Effects of high-intensity resistance training on circulating levels of irisin in healthy adults: a randomized controlled trial,” Asian Journal of Sports Medicine, vol. 9, no. 2, 2018.

[24] F. Izaddoust and R. Shabani, Effects of Strength Training on Serum Levels of Irisin and Myostatin Hormones, and Their Association with Lipid Profiles in Untrained Women, 2017.

[25] B. Kabak, M. Belviranli, and N. Okudan, "Irisin and myostatin responses to acute high-intensity interval exercise in humans," Hormone molecular biology and clinical investigation, vol. 35, no. 3, 2018.

[26] E. Miyamoto-Mikami, K. Sato, T. Kurihara 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, vol. 10, no. 3, article e0120354, 2015.

[27] E. Muraw ska-Ciałowicz, P. Wolanski, J. Zuwala-Jagiello et al., “Effect of HITT with Tabata protocol on serum irisin, physical performance, and body composition in men,” International Journal of Environmental Research and Public Health, vol. 17, no. 10, p. 3589, 2020.

[28] C. Nicollini, B. Michalski, S. L. Toepf et al., “A single bout of high-intensity interval exercise increases cortisopinal excitability, brain-derived neurotrophic factor, and uncarboxylated osteocalcin in sedentary, healthy males,” Neuroscience, vol. 437, pp. 242–255, 2020.

[29] S. Qiu, E. Bosnyák, G. Trefl et al., “Acute exercise-induced irisin release in healthy adults: associations with training status and exercise mode,” European journal of sport science, vol. 18, no. 9, pp. 1226–1233, 2018.

[30] E. Rodziewicz, M. Król-Zielinska, J. Zielinski, K. Kusy, and E. J. F. Ziemann, “Plasma concentration of irisin and brain-derived-neurotrophic factor and their association with the level of erythrocyte adenine nucleotides in response to long-term endurance training at rest and after a single bout of exercise,” Frontiers in Physiology, vol. 11, p. 923, 2020.

[31] F. Rostami and R. Shabani, “The effect of eight weeks aerobic training on serum irisin, glucose homeostasis and blood lipid levels in untrained women,” Journal of Sabzevar University of Medical Sciences, vol. 26, pp. 185–193, 2019.

[32] R. Shabani and F. J. A. G. Izadoud, “Effects of aerobic training, resistance training, or both on circulating irisin and myostatin in untrained women,” Acta Gymnica, vol. 48, no. 2, pp. 47–55, 2018.

[33] S. Chireh, R. Alizadeh, L. J. S. P. Moradi, and M. Investigations, “The effect of 3 weeks ergometer cycling training with and without vascular occlusion on plasma concentration of irisin and PGC-1α in healthy men,” Sport Physiology & Management Investigations, vol. 9, pp. 95–105, 2018.

[34] H. J. Kim, B. So, M. Choi, D. Kang, and W. Song, “Resistance exercise training increases the expression of irisin concomitant with improvement of muscle function in aging mice and humans,” Experimental gerontology, vol. 70, pp. 11–17, 2015.

[35] J. Zhao, Z. Su, C. Qu, and Y. Dong, “Effects of 12 weeks resistance training on serum irisin in older male adults,” Frontiers in Physiology, vol. 8, p. 171, 2017.

[36] J. M. Moreno-Navarrete, F. Ortega, M. Serrano et al., “Irisin is expressed and produced by human muscle and adipose tissue in association with obesity and insulin resistance,” The Journal of Clinical Endocrinology & Metabolism, vol. 98, no. 4, pp. E769–E778, 2013.

[37] A. Rocarivada, C. Castelao, L. L. Senin et al., “FND5C/irisin is not only a myokine but also an adipokine,” PloS one, vol. 8, no. 4, article e60563, 2013.

[38] W. C. Miller, D. Koceja, and E. Hamilton, “A meta-analysis of the past 25 years of weight loss research using diet, exercise or diet plus exercise intervention,” International journal of obesity, vol. 21, no. 10, pp. 941–947, 1997.

[39] N. M. Pimenta, H. Santa-Clar a, L. B. Sardinha, and B. Fernhall, “Body fat responses to a 1-year combined exercise training program in male coronary artery disease patients,” Obesity, vol. 21, no. 4, pp. 723–730, 2013.

[40] K. Hee Park, I. Zaichenko, M. Brinkoetter et al., “Circulating irisin in relation to insulin resistance and the metabolic syndrome,” The Journal of Clinical Endocrinology & Metabolism, vol. 98, no. 12, pp. 4899–4907, 2013.

[41] G. Sesti, F. Andreozzi, T. Fiorentino et al., “High circulating irisin levels are associated with insulin resistance and vascular atherosclerosis in a cohort of nondiabetic adult subjects,” Acta diabetologica, vol. 51, no. 5, pp. 705–713, 2014.

[42] N. M. Al-Daghri, K. M. Alkhayr, S. Rahman et al., “Irisin as a predictor of glucose metabolism in children: sexually dimorphic effects,” European Journal of Clinical Investigation, vol. 44, no. 2, pp. 119–124, 2014.

[43] G. P. Nassis, K. Papantakou, K. Skenderi et al., “Aerobic exercise training improves insulin sensitivity without changes in body weight, body fat, adiponectin, and inflammatory markers.
in overweight and obese girls,” *Metabolism*, vol. 54, no. 11, pp. 1472–1479, 2005.

[44] R. A. Vaughan, N. P. Gannon, C. M. Mermier, and C. A. Conn, “Irisin, a unique non-inflammatory myokine in stimulating skeletal muscle metabolism,” *Journal of physiology and biochemistry*, vol. 71, no. 4, pp. 679–689, 2015.

[45] A. G. Swick, S. Orena, and A. O’Connor, “Irisin levels correlate with energy expenditure in a subgroup of humans with energy expenditure greater than predicted by fat free mass,” *Metabolism*, vol. 62, no. 8, pp. 1070–1073, 2013.

[46] J. E. Donnelly, S. D. Herrmann, K. Lambourne, A. N. Szabo, J. J. Honas, and R. A. Washburn, “Does increased exercise or physical activity alter ad-libitum daily energy intake or macronutrient composition in healthy adults? A systematic review,” *PloS one*, vol. 9, no. 1, article e83498, 2014.

[47] C. Martins, D. Stensvold, G. Finlayson et al., “Effect of moderate- and high-intensity acute exercise on appetite in obese individuals,” *Medicine and Science in Sports and Exercise*, vol. 47, no. 1, pp. 40–48, 2015.

[48] E. Tsiani, N. Tsakiridis, R. Kouvelioti, A. Jaglanian, and P. Klentrou, “Current evidence of the role of the myokine irisin in cancer,” *Cancers*, vol. 13, no. 11, p. 2628, 2021.

[49] A. D. Anastasilakis, S. A. Polyzos, Z. G. Saridakis et al., “Circulating irisin in healthy, young individuals: day-night rhythm, effects of food intake and exercise, and associations with gender, physical activity, diet, and body composition,” *The Journal of Clinical Endocrinology & Metabolism*, vol. 99, no. 9, pp. 3247–3255, 2014.

[50] Q. Ruan, Y. Huang, L. Yang et al., “The effects of both age and sex on irisin levels in paired plasma and cerebrospinal fluid in healthy humans,” *Peptides*, vol. 113, pp. 41–51, 2019.