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Review

Exercise training mode effects on myokine expression in healthy adults: A systematic review with meta-analysis

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Abstract

Background: The benefits of exercise are well known; however, many of the underlying molecular mechanisms are not fully understood. Skeletal muscle secretes myokines, which mediate muscle–organ crosstalk. Myokines regulate satellite-cell proliferation and migration, inflammatory cascade, insulin secretion, angiogenesis, fatty oxidation, and cancer suppression. To date, the effects of different exercise modes (namely, aerobic and resistance exercise) on myokine response remain to be elucidated. This is crucial considering the clinical implementation of exercise to enhance general health and wellbeing and as a medical treatment.

Methods: A systematic search was undertaken in PubMed, MEDLINE, CINAHL, Embase, SPORTDiscus, and Web of Science in April 2023. Eligible studies examining the effects of a single bout of exercise on interleukin15 (IL-15), irisin, secreted protein acidic and rich in cysteine (SPARC), oncostatin M (OSM), and decorin were included. A random-effects meta-analysis was also undertaken to quantify the magnitude of change.

Results: Sixty-two studies were included ($n = 1193$). Overall, exercise appeared to induce small to large increases in myokine expression, with effects observed immediately after to 60 min post-exercise, although these were mostly not statistically significant. Both aerobic and resistance exercise resulted in changes in myokine levels, without any significant difference between training modes, and with the magnitude of change differing across myokines. Myokine levels returned to baseline levels within 180 min to 24 h post-exercise. However, owing to potential sources of heterogeneity, most changes were not statistically significant, indicating that precise conclusions cannot be drawn.

Conclusion: Knowledge is limited but expanding with respect to the impact of overall and specific effects of exercise on myokine expression at different time points in the systemic circulation. Further research is required to investigate the effects of different exercise modes at multiple time points on myokine response.

Keywords: Myokine; Resistance exercise; Aerobic exercise; Cytokine; Systemic circulation

1. Introduction

The World Health Organization defines physical activity as any bodily movement produced by skeletal muscles that requires energy expenditure.[1] The World Health Organization expert panel recommends at least 150–300 min or 75–150 min of moderate or vigorous aerobic physical activity, respectively, and strengthening exercises involving all major muscle groups at moderate or high intensity at least twice per week.[1] Exercise is a subset of physical activity that is planned, structured, and repetitive and aims to improve markers of fitness and health, including muscle strength, cardiorespiratory fitness, bone density, body weight, reduced risk of depression, and so on.[1] Additionally, exercise can prevent the possible onset of noncommunicable diseases, including cardiovascular diseases, chronic respiratory

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diseases, type 2 diabetes mellitus, and cancer.[1] For these reasons, there is a growing interest in exercise for general health and well-being and, most recently, as a medical treatment.[1,2]

Although the benefits of exercise are well known, not all the underlying molecular mechanisms are fully understood. Skeletal muscle, which accounts for approximately 40% of total body weight, is recognized as an endocrine organ.[3,4] Indeed, during muscular contractions, skeletal muscle cells secret cytokines called myokines into circulation to exert either paracrine, autocrine, or endocrine effects.[5–8] From a biological perspective, not only are myokines involved in the regulation of muscle metabolism, but they also mediate crosstalk between muscle and organs, including adipose tissue, bone, the liver, the gut, the pancreas, and the brain.[6,9–11] Myokines are implicated in several processes, including satellite-cell proliferation and migration, control of inflammatory cascade and insulin secretion, regulation of angiogenesis and fatty oxidation, and importantly, direct anti-cancer defense (e.g., reducing cancer cell growth).[12,13] As more than 600 myokines have been identified to date, and the role of most of them remains unknown,[6] this review will focus on exercise-induced myokines with established effects on the human body, including interleukin 15 (IL-15), secreted protein acidic and rich in cysteine (SPARC), irisin, oncostatin M (OSM), and decorin.

Briefly, exercise-induced myokine IL-15 contributes to the regulation of muscle mass with its anabolic effects; it is also capable of influencing adipogenesis, reducing adipocyte proliferation and differentiation, altering adipocyte size and number, and promoting apoptosis.[14,15] Additionally, the myokine irisin contributes to the browning of white adipose tissue and is essential for regulating glucose, lipid, and energy homeostasis.[16] Recently, it has been proposed that irisin may also have pro-myogenic effects in skeletal muscle.[17] SPARC is another myokine that plays a pivotal role in muscle metabolism, augmenting fatty acid oxidation and glucose uptake and stimulating insulin sensitivity.[18,19] Similarly, exercise-induced OSM has also been proposed to mediate muscle hypertrophy, although further research is necessary.[20] Lastly, decorin is considered a candidate in inducing protein synthesis, which leads to muscle growth.[21,22] The role of these myokines in both the prevention and treatment of cancer is particularly interesting. SPARC, irisin, OSM, and decorin have been demonstrated to have potential direct cancer suppressive effects, while IL-15 appears to be an immunomodulator candidate for cancer.[13,23–25] Therefore, a better understanding of these myokines and how they respond to exercise appears to be an important line of investigation for both healthy individuals and for those suffering from disease.

From a physiological perspective, preliminary evidence shows that benefits driven by exercise-induced myokines are the result of an accumulation of single bouts of exercise rather than chronic exposure to exercise training programs.[26] Therefore, it seems logical to investigate the effects of a single bout of exercise on myokine expression. Although it has been postulated that muscular contractions increase myokine levels in the bloodstream, contradictory results have been found, indicating that more research is necessary to clearly elucidate the effects of a single bout of exercise on myokine expression.[27] In addition, and of utmost importance, the effects of different exercise modes on myokine response remain to be clarified. Indeed, to date, 2 distinct modes are commonly used, namely aerobic exercise (AE) and resistance exercise (RE).[28] This is significant considering the clinical implementation of precise exercise prescription (i.e., AE or RE) to enhance general health and wellbeing and as a form of medical treatment (e.g., cancer-suppressive effects of exercise).[13]

To the best of our knowledge, no systematic reviews or meta-analyses have been conducted to explore either the effects of a single bout of exercise on IL-15, SPARC, OSM, and decorin expression nor the potential differential effects by exercise mode. Although recent reviews have been reported on the effects of a single bout of exercise on the acute irisin response (i.e., immediately after exercise),[29–31] our meta-analysis is the first to examine the effects of different exercise modes across different time points (i.e., up to 24 h after exercise). Thus, the aims of this systematic review with meta-analysis were 3-fold: (a) to examine the overall effects of a single bout of exercise on IL-15, irisin, SPARC, OSM, and decorin expression in healthy adults; (b) to determine the effects of different exercise modes (i.e., AE, RE, and combined) on myokine responses; and (c) to investigate changes in myokine expression at different time points (i.e., from immediately up to 24 h) after a single bout of exercise.

2. Methods

2.1. Search strategy and study selection procedure

All procedures were conducted in compliance with the guidelines outlined by the Cochrane Back Review Group,[32] adhering to the reporting standards established in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (Fig. 1),[33,34] and registered with the International Prospective Register of Systematic Reviews (PROSPERO: CRD42023414177). The search was conducted in MEDLINE (via PubMed), CINAHL, Embase, SPORTDiscus (via EBSCOhost), and Web of Science in April 2023. A manual search was undertaken in the reference lists provided in all retrieved studies. Eligibility was assessed independently by 2 reviewers (FB and AMM) and evaluated by a third reviewer in case of disagreement (JSK). The search strategy is presented in the Supplementary File (Search terms).

2.2. Eligibility criteria

For the current review, we included randomized or non-randomized clinical trials, cross-over (>72 h wash-out period), and single-group studies investigating the effects of AE, RE or combined AE and RE on myokine expression. Primary outcomes were changes in the myokine expression (including IL-15, irisin, SPARC, OSM, and decorin) immediately after; 30 min, 60 min, 120 min, or 180 min; or 24 h after a single bout of AE, RE, or combined exercise. The inclusion criteria were sedentary, physically active, or trained adults (≥18 years) randomized or enrolled to perform a single bout of

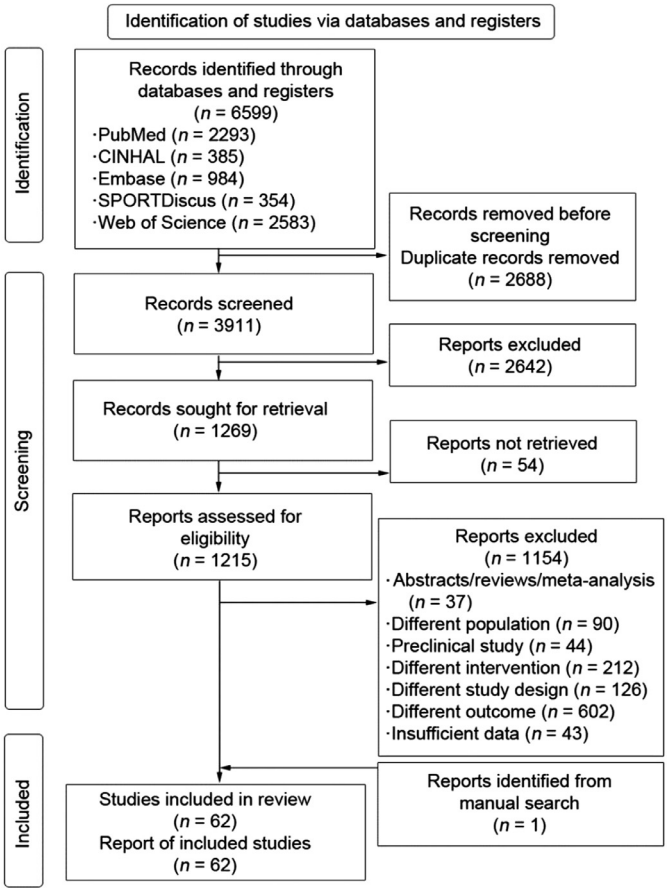

Fig. 1. Flow chart of study selection process.

exercise. Exclusion criteria were: (a) studies involving participants with chronic conditions (e.g., type 2 diabetes, cancer, *etc*.); (b) body mass index (BMI) > 30 kg/m^2; (c) studies with no precise indications regarding volume and intensity and different exposure for each subject participating (e.g., marathon or football matches); (d) studies including any other intervention coupled with exercise (e.g., diet, cold or heat exposure); and (e) studies written in a language other than English.

2.3. Data extraction

Data extraction was performed by 2 independent authors (FB and AMM). Study information, including sample size, gender, physical status, age, BMI, study design, and training intervention were extracted along with the outcomes of interest. For the outcomes examined, baseline and post-intervention assessments were extracted in their absolute units, inclusive of mean and standard deviation (SD). When graphs were used instead of numerical data, we assessed graphs by analyzing their plots using a specific tool for data extraction (Version 4.7; WebPlotDigitizer, San Francisco, CA, USA).[35] As initially planned, the TESTEX scale was selected to assess the risk of bias.[36] It should be noted that the TESTEX scale is used to investigate items for chronic training interventions, including allocation concealment, blinding of participants and assessors, outcomes measured in 85% of subjects, between-group statistical comparison, monitoring of the control group, and constancy of exercise intensity during the interventions. However, the current review looks at studies examining a single bout of exercise (and often lacking a control group), meaning the majority of included studies adopted a single group assessment of within-group pre and post changes (Supplementary Table 1). Consequently, most of the items in the original TESTEX scale were inappropriate. Therefore, the authors decided not to use the risk of bias tool, which is in line with previous reviews investigating the effects of a single bout of exercise.[37–39] This highlights the fact that there is currently no validated scale for acute studies.

2.4. Statistical analysis

A 3-level mixed-effects meta-analysis with study included as a random effect was performed to examine the acute effects of a single bout of exercise on myokine response. A minimum of 2 studies were required to run a meta-analysis for each myokine at a given time point. Given the availability of several dependent outcomes from the same study, a robust variance estimation approach was undertaken to account for the nested structure of the effect sizes calculated from the studies included (i.e., effects nested within categories nested within studies).[40] The pooled effect estimated from the outcomes of interest was obtained from within-group mean difference (MD) and expressed as the standardized MD (SMD). Cluster robust point estimates 95% confidence intervals (95%CIs) were reported, weighted by inverse sampling variance to account for the within- and between-study variance (τ^2). In addition, restricted maximal-likelihood estimation was used in all models. The criterion for statistical significance was set at $p < 0.05$. According to Hedges' g, SMD values of 0.00 to ≤0.50 indicate small, >0.50 to 0.79 moderate, and ≥0.80 large effects.[41]

Statistical heterogeneity was assessed using the Cochran Q test. A threshold p value of 0.1 and values greater than 50% in I^2 were considered indicative of high heterogeneity. Publication bias was explored by contour-enhanced funnel plots and Egger's test when more than 10 studies were available.[42] Subgroup analyses were provided for: (a) different exercise modes (i.e., AE, RE, and combined exercise); (b) different time points, from immediately after (i.e., within 10 min from blood collection) to 24 h after; and (c) different physical activity statuses (i.e., sedentary, physically active, trained) when available. A meta-regression was also undertaken to quantify the association of age with changes in outcomes of interest when more than 10 studies were available.[42]

Analyses were conducted using the package metafor and clubSandwich from R (R Core Team, Version, 4.0.3., 2020; R Foundation for Statistical Computing, Vienna, Austria).[43]

3. Results

A total of 6599 studies were retrieved from our search, with 3911 potential records retained for screening after duplicate removals. After excluding 2642 records due to their irrelevance to the research question, 1215 were considered eligible for full-text assessment (Fig. 1). A total of 62 articles

investigating the effects of AE, RE, or combined exercise on IL-15, irisin, SPARC, OSM, or decorin expression at different time points were subsequently included in the meta-analyses.[44–105]

3.1. Participants and intervention characteristics

A total of 1193 healthy adults participated in the included studies; median age was 29.74 years (interquartile range: 22.3–29.9 years) and median BMI was 23.64 kg/m^2 (interquartile range: 22.1–24.8 kg/m^2). Among the participants, there were 676 men and 227 women, as well as 290 participants whose gender was not reported. From the 62 studies, a total of 240, 267, and 379 subjects were classed as trained, physically active, and sedentary, respectively, while physical fitness status was not stated for 307 subjects. In regard to the exercise modes, a single bout of AE, RE, and combined exercise was used in 48, 17, and 2 interventions, respectively (Supplementary Table 1).[44–105]

For AE, which included running, cycling, and rowing, moderate intensity continuous AE (MICAE) and high intensity AE (HIAE; encompassing both incremental test to exhaustion and high intensity interval training) were used in 29 and 21 interventions, respectively.[44,46,47,51–61,64,66,68–71,73–86,89–94,96,97,100–105] Training duration (e.g., minutes) and intensity (e.g., maximal oxygen consumption (VO_{2max})) for AE was reported in 45 and 48 interventions, respectively. MICAE duration ranged from 20 to 180 min with an intensity set from 40% to 80% VO_{2max}, 60% to 110% maximal heart rate, or 40% to 70% heart rate reserve ($HR_{reserve}$). For HIAE, the duration of the higher intensity bouts ranged from 20 s to 5 min with an intensity from 57% to 64% maximal heart rate, 70% to 75% $HR_{reserve}$, or maximal effort. Additionally, some interventions performed an incremental bout of HIAE to exhaustion without any bout at lower intensity.

For RE, 17 interventions utilized traditional RE, 2 used cluster sets and concentric RE separately, and there was 1 intervention each for eccentric and isometric RE.[45,48–50,58,63,65,67,70,72,83,87,88,95,98,99,102] Volume in terms of sets and repetitions ranged from 1 to 5 sets and from 5 to 30 repetitions with intensity from 30% to 100% of 1-repetition maximum (1RM); apart from 2 interventions where RE to volitional exhaustion was adopted. The number of exercises ranged from 1 to 10 across all interventions.

Regarding combined AE and RE, 2 interventions were found including RE (i.e., 3 sets of 12 repetitions at 65% 1RM), AE (i.e., 30 min at 65% VO_{2max}), and multimodal exercise (i.e., jogging, gymnastics, and sprints).[62,83]

In the following sub-headings, we reported the overall effects of a single bout of exercise and, when available, the effects of a single bout of AE, RE, or combined exercise. Similarly, when available, we recorded each time point from immediately after up to 24 h after the single bout of exercise. Additionally, it should be noted that the number of studies and effect sizes for each exercise mode may differentiate from the overall effect. This comes from the fact that meta-analyses were performed only if sufficient data for each exercise mode were available.

3.2. IL-15

3.2.1. Main model effects, sensitivity analysis, and subgroup analysis

3.2.1.1. Main model. Twenty studies and 74 effect sizes were undertaken for the IL-15 model[45,48,50,52,58,61,63,64,66,72,74,77,80,90,92,93,95,97–99] (Table 1). When examining the main model effect, a non-significant large increase was found (SMD = 0.95; 95%CI: −0.23 to 2.13; $p = 0.11$). The heterogeneity I^2 was 46.70% with an effect of publication bias ($t = 5.3$; $p < 0.001$). No statistically significant differences between AE and RE ($p = 0.10$) (Supplementary Table 2) or by different physical activity status (SMD: 0.07–1.28; p: 0.22–0.48) (Supplementary Table 3) were observed. In addition, age was not significantly associated with changes in IL-15 ($\beta = -0.008 \pm 0.020$; $p = 0.73$) (Supplementary Fig. 1).

3.2.1.2. Immediately after. Twenty studies and 34 effect sizes were undertaken for IL-15 expression immediately after a single bout of exercise compared to baseline[45,48,50,52,58,61,63,64,66,72,74,77,80,90,92,93,95,97–99] (Table 1 and Fig. 2). When examining the overall effect, a non-significant large increase was found (SMD = 1.14; 95%CI: −0.21 to 2.49; $p = 0.09$). For AE a non-significant small increase was found (SMD = 0.17; 95%CI: −0.27 to 0.60; $p = 0.41$) while for RE a non-significant large increase was found (SMD = 2.66; 95%CI: −0.67 to 5.99; $p = 0.10$). No statistically significant differences between AE and RE were observed ($p = 0.08$) (Supplementary Table 2).

3.2.1.3. 30 min after. Four studies and 8 effect sizes were undertaken for IL-15 expression 30 min after a single bout of exercise compared to baseline[58,63,95,99] (Table 1). When examining the overall effect, a non-significant large increase was found (SMD = 1.64; 95%CI: −2.92 to 6.20; $p = 0.33$). For RE, a non-significant large increase was found (SMD = 1.48; 95%CI: −3.30 to 6.26; $p = 0.40$). The other effect sizes were composed by AE from the same study, preventing meta-analysis from being performed.

3.2.1.4. 60 min after. Ten studies and 15 effect sizes were undertaken for IL-15 expression 60 min after a single bout of exercise compared to baseline[48,61,63,66,80,90,93,95,98,99] (Table 1). When examining the overall effect, a non-significant large increase was found (SMD = 1.49; 95%CI: −0.85 to 3.83; $p = 0.18$). For AE there was no effect (SMD = 0.01; 95%CI: −0.23 to 0.22; $p = 0.95$) while for RE a non-significant large increase was found (SMD = 3.11; 95%CI: −2.47 to 8.69; $p = 0.20$). No statistically significant differences between AE and RE were observed ($p = 0.12$) (Supplementary Table 2).

3.2.1.5. 120 min after. Two studies and 2 effect sizes were undertaken for IL-15 expression 120 min after a single bout of exercise compared to baseline[93,95] (Table 1). When examining

Table 1
Effects of single bouts of exercise on IL-15 expression.

Main model	K	No. of ES	Random-effect meta-analysis			Heterogeneity		
			ES	95%CI	*p*	*Q*	I^2	*p*
Main model effect	20	74	0.95	−0.23 to 2.13	0.11	399.10	46.70	0.001
Time points								
Immediately after								
Overall effect	20	34	1.14	−0.21 to 2.49	0.09	162.90	47.40	0.001
Aerobic exercise	12	17	0.17	−0.27 to 0.60	0.41	17.40	13.20	0.360
Resistance exercise	9	17	2.66	−0.67 to 5.99	0.10	134.90	48.80	0.001
Aerobic + resistance exercise	NA							
30 min								
Overall effect	4	8	1.64	−2.92 to 6.20	0.33	39.10	47.20	0.001
Aerobic exercise	NA							
Resistance exercise	4	6	1.48	−3.30 to 6.26	0.40	37.00	47.40	0.001
Aerobic + resistance exercise	NA							
60 min								
Overall effect	10	15	1.49	−0.85 to 3.83	0.18	96.50	47.70	0.001
Aerobic exercise	5	6	0.01	−0.23 to 0.22	0.95	2.60	0	0.760
Resistance exercise	5	9	3.11	−2.47 to 8.69	0.20	91.00	49.70	0.001
Aerobic + resistance exercise	NA							
120 min								
Overall effect	2	2	3.69	−40.72 to 48.10	0.48	28.10	48.20	0.001
Aerobic exercise	NA							
Resistance exercise	NA							
Aerobic + resistance exercise	NA							
180 min								
Overall effect	4	4	0	−0.32 to 0.32	0.98	0.50	0	0.920
Aerobic exercise	4	4	0	−0.32 to 0.32	0.98	0.50	0	0.920
Resistance exercise	NA							
Aerobic + resistance exercise	NA							
24 h								
Overall effect	7	11	1.35	−1.29 to 3.98	0.26	55.10	47.60	0.001
Aerobic exercise	2	2	0.34	−3.46 to 4.14	0.46	0.60	0	0.420
Resistance exercise	5	9	1.72	−2.66 to 6.10	0.34	54.40	48.30	0.001
Aerobic + resistance exercise	NA							

Abbreviations: 95%CI = 95% confidence interval; ES = effect size; I^2 = percentage of variation across studies that is due to heterogeneity; IL-15 = interleukin15; K = number of studies; NA = not available; *Q* = Cochran's *Q* test of heterogeneity.

the overall effect, a non-significant large increase was found (SMD = 3.69; 95%CI: −40.72 to 48.10; $p = 0.48$). The effect sizes were composed by 1 AE and 1 RE.

3.2.1.6. 180 min after. Four studies and 4 effect sizes were undertaken for IL-15 expression 180 min after a single bout of exercise compared to baseline[74,77,80,93] (Table 1). When examining the overall effect, a non-significant change was found (SMD = 0; 95%CI: −0.32 to 0.32; $p = 0.98$). As the studies only included AE, results are the same when subgrouping by exercise mode.

3.2.1.7. 24 h after. Seven studies and 11 effect sizes were undertaken for IL-15 expression 24 h after a single bout of exercise compared to baseline[63,72,74,93,95,98,99] (Table 1). When examining the overall effect, a non-significant large increase was found (SMD = 1.35; 95%CI: −1.29 to 3.98; $p = 0.26$). For AE a non-significant small increase was found (SMD = 0.34; 95%CI: −3.46 to 4.14; $p = 0.46$) while for RE a non-significant large increase was found (SMD = 1.72; 95%CI: −2.66 to 6.10; $p = 0.34$). No statistically significant differences between AE and RE were observed ($p = 0.39$) (Supplementary Table 2).

3.3. Irisin

3.3.1. Main model effects, sensitivity analysis, and subgroup analysis

3.3.1.1. Main model. Thirty-six studies and 110 effect sizes were undertaken for the irisin model[44,46,47,49,54–57,59,60,62,65,67–71,73,76,78,81–86,88,89,91,94,96,100–103,105] (Table 2). When examining the main model effect, a non-significant small increase was found (SMD = 0.44; 95%CI: −0.04 to 0.91; $p = 0.07$). The heterogeneity I^2 was 40.20% with no effect of publication bias ($t = -0.1$; $p = 0.92$). No statistically significant differences between AE and RE ($p = 0.38$) (Supplementary Table 2) or by different physical activity status (SMD: 0.24−1.24; *p*: 0.23−0.30) (Supplementary Table 3) were observed. In addition, age was not significantly associated with changes in irisin ($\beta = 0.01 \pm 0.01$; $p = 0.57$) (Supplementary Fig. 2).

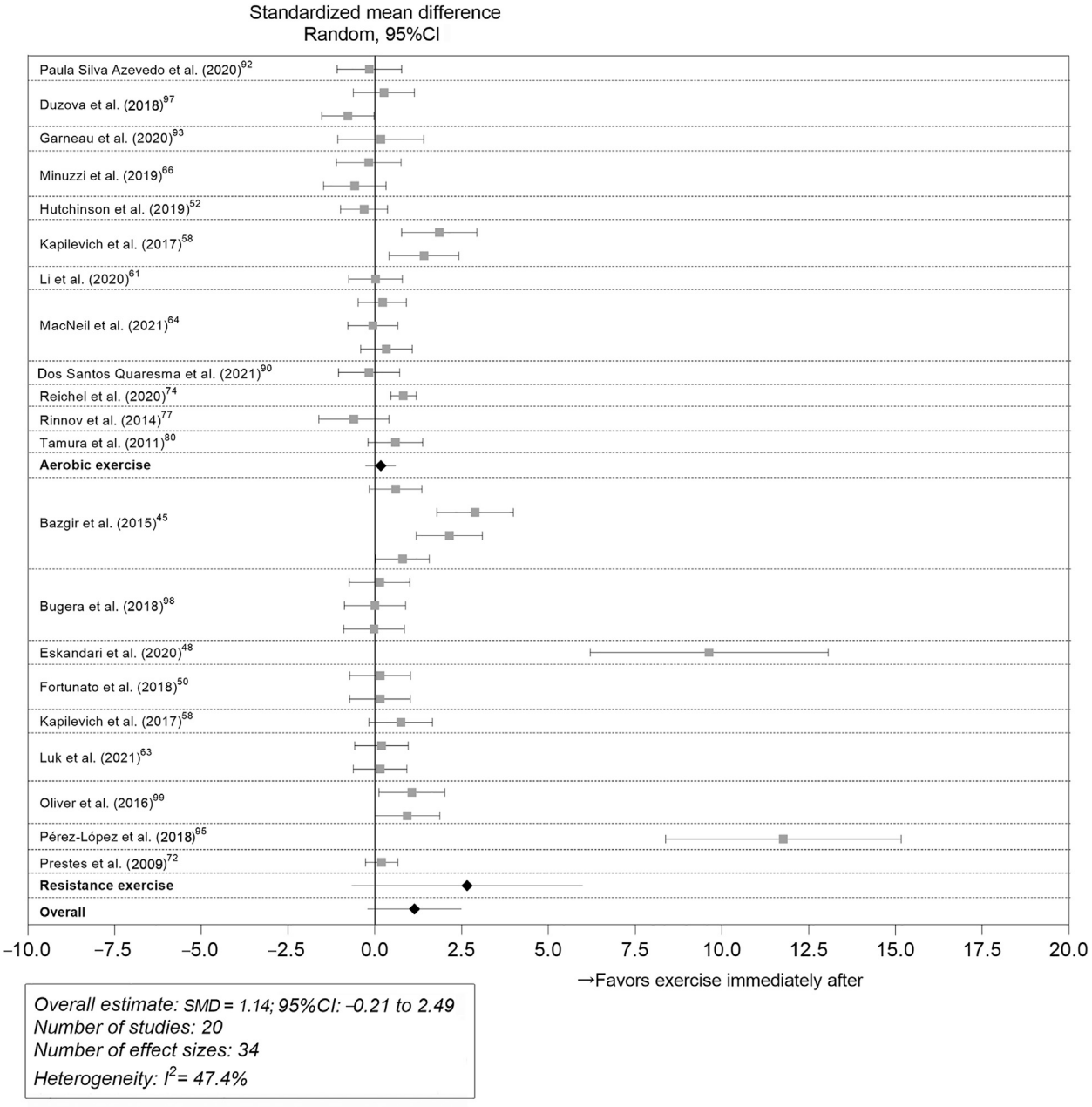

Fig. 2. Forest plot of overall and specific effects on IL-15 expression immediately following a single bout of exercise. 95%CI = 95% confidence interval; I^2 = heterogeneity test; IL-15 = interleukin15; SMD = standardized mean difference.

3.3.1.2. Immediately after. Thirty-four studies and 58 effect sizes were undertaken for irisin expression immediately after a single bout of exercise compared to baseline[44,46,47,49,54–57,59,60,62,65,67–71,73,76,78,81–86,88,89,91,94,100–103] (Table 2 and Fig. 3). When examining the overall effect, a non-significant small increase was found (SMD = 0.50; 95%CI: −0.22 to 1.22; $p = 0.17$). For AE a non-significant moderate increase was found (SMD = 0.63; 95%CI: −0.30 to 1.56; $p = 0.18$) while for RE a non-significant small increase was found (SMD = 0.10; 95%CI: −0.29 to 0.48; $p = 0.55$). When examining the effect of combined exercise, a non-significant small increase was found (SMD = 0.26; 95%CI: −0.42 to 0.94; $p = 0.13$). No statistically significant differences between AE and RE were observed ($p = 0.39$) (Supplementary Table 2).

3.3.1.3. 30 min after. Eleven studies and 17 effect sizes were undertaken for irisin expression 30 min after a single bout of exercise compared to baseline[55,56,62,65,76,83,86,94,96,102,105] (Table 2). When examining the overall effect, a non-significant moderate increase was found (SMD = 0.81; 95%CI: −0.35 to 1.98; $p = 0.15$). For AE a non-significant large increase was found (SMD = 1.18; 95%CI: −0.52 to 2.87; $p = 0.14$) while for RE a non-significant small increase was found (SMD = 0.02; 95%CI: −0.31 to 0.35; $p = 0.81$). When investigating the effect of combined exercise, a non-significant small increase

Table 2
Effects of single bouts of exercise on irisin expression.

Main model	K	No. of ES	Random-effect meta-analysis			Heterogeneity		
			ES	95%CI	*p*	*Q*	I^2	*p*
Main model effect	36	110	0.44	−0.04 to 0.91	0.07	279.10	40.20	0.001
Time points								
Immediately after								
Overall effect	34	58	0.50	−0.22 to 1.22	0.17	200.90	45.20	0.001
Aerobic exercise	28	46	0.63	−0.30 to 1.56	0.18	197.40	46.50	0.001
Resistance exercise	7	9	0.10	−0.29 to 0.48	0.55	2.00	0	0.98
Aerobic + resistance exercise	2	3	0.26	−0.42 to 0.94	0.13	0.10	0	0.94
30 min								
Overall effect	11	17	0.81	−0.35 to 1.98	0.15	61.40	42.70	0.001
Aerobic exercise	8	11	1.18	−0.52 to 2.87	0.14	56.10	44.60	0.001
Resistance exercise	3	3	0.02	−0.31 to 0.35	0.81	0.10	0	0.96
Aerobic + resistance exercise	2	3	0.13	−4.71 to 4.97	0.79	0.90	0	0.65
60 min								
Overall effect	7	12	0.38	0.05 to 0.71	0.03	3.10	0	0.99
Aerobic exercise	6	8	0.40	−0.01 to 0.81	0.05	1.50	0	0.98
Resistance exercise	3	3	0.32	−1.21 to 1.85	0.47	1.60	0	0.45
Aerobic + resistance exercise	NA							
120 min								
Overall effect	5	8	0.09	−0.21 to 0.39	0.40	1.30	0	0.99
Aerobic exercise	4	4	0.01	−0.33 to 0.34	0.94	0.40	0	0.95
Resistance exercise	3	3	0.09	−0.71 to 0.88	0.69	0.50	0	0.79
Aerobic + resistance exercise	NA							
180 min								
Overall effect	6	11	−0.14	−0.75 to 0.46	0.55	4.20	1.90	0.94
Aerobic exercise	6	9	−0.26	−0.76 to 0.24	0.23	2.70	0	0.95
Resistance exercise	NA							
Aerobic + resistance exercise	NA							
24 h								
Overall effect	2	4	0.05	−0.80 to 0.89	0.61	0.40	0	0.94
Aerobic exercise	2	3	−0.01	−2.25 to 2.24	0.97	0.30	0	0.86
Resistance exercise	NA							
Aerobic + resistance exercise	NA							

Abbreviations: 95%CI = 95% confidence interval; ES = effect size; I^2 = percentage of variation across studies that is due to heterogeneity; K = number of studies; NA = not available; *Q* = Cochran's *Q* test of heterogeneity.

was found (SMD = 0.13; 95%CI: −4.71 to 4.97; $p = 0.79$). No statistically significant differences between AE and RE were observed ($p = 0.26$) (Supplementary Table 2).

3.3.1.4. 60 min after. Seven studies and 12 effect sizes were undertaken for irisin expression 60 min after a single bout of exercise compared to baseline[65,70,83,84,86,89,102] (Table 2). When examining the overall effect, a significant small increase was found (SMD = 0.38; 95%CI: 0.05−0.71; $p = 0.03$). For AE a significant small increase was found (SMD = 0.40; 95%CI: −0.01 to 0.81; $p = 0.05$); similarly, for RE a non-significant small increase was found (SMD = 0.32; 95%CI: −1.21 to 1.85; $p = 0.47$). No statistically significant differences between AE and RE were observed ($p = 0.83$) (Supplementary Table 2).

3.3.1.5. 120 min after. Five studies and 8 effect sizes were undertaken for irisin expression 120 min after a single bout of exercise compared to baseline[65,69,70,83,84] (Table 2). When examining the overall effect, a non-significant small increase was found (SMD = 0.09; 95%CI: −0.21 to 0.39; $p = 0.40$). For AE there was no effect (SMD = 0.01; 95%CI: −0.33 to 0.34; $p = 0.94$); similarly, for RE a non-significant small increase was found (SMD = 0.09; 95%CI: −0.71 to 0.88; $p = 0.69$). No statistically significant differences between AE and RE were observed ($p = 0.71$) (Supplementary Table 2).

3.3.1.6. 180 min after. Six studies and 11 effect sizes were undertaken for irisin expression 180 min after a single bout of exercise compared to baseline[46,57,73,82–84] (Table 2). When examining the overall effect, a non-significant small decrease was found (SMD = −0.14; 95%CI: −0.75 to 0.46; $p = 0.55$). For AE a non-significant small decrease was found (SMD = −0.26; 95%CI: −0.76 to 0.24; $p = 0.23$). The other effect sizes were composed by RE from the same study, preventing meta-analysis from being performed.

3.3.1.7. 24 h after. Two studies and 4 effect sizes were undertaken for irisin expression 24 h after a single bout of exercise compared to baseline[70,86] (Table 2). When examining the overall effect, there was no effect (SMD = 0.05; 95%CI: −0.80 to 0.89; $p = 0.61$). For AE there was no effect (SMD = −0.01; 95%CI: −2.25 to 2.24; $p = 0.97$). The other effect sizes were composed by RE from the same study, preventing meta-analysis from being performed.

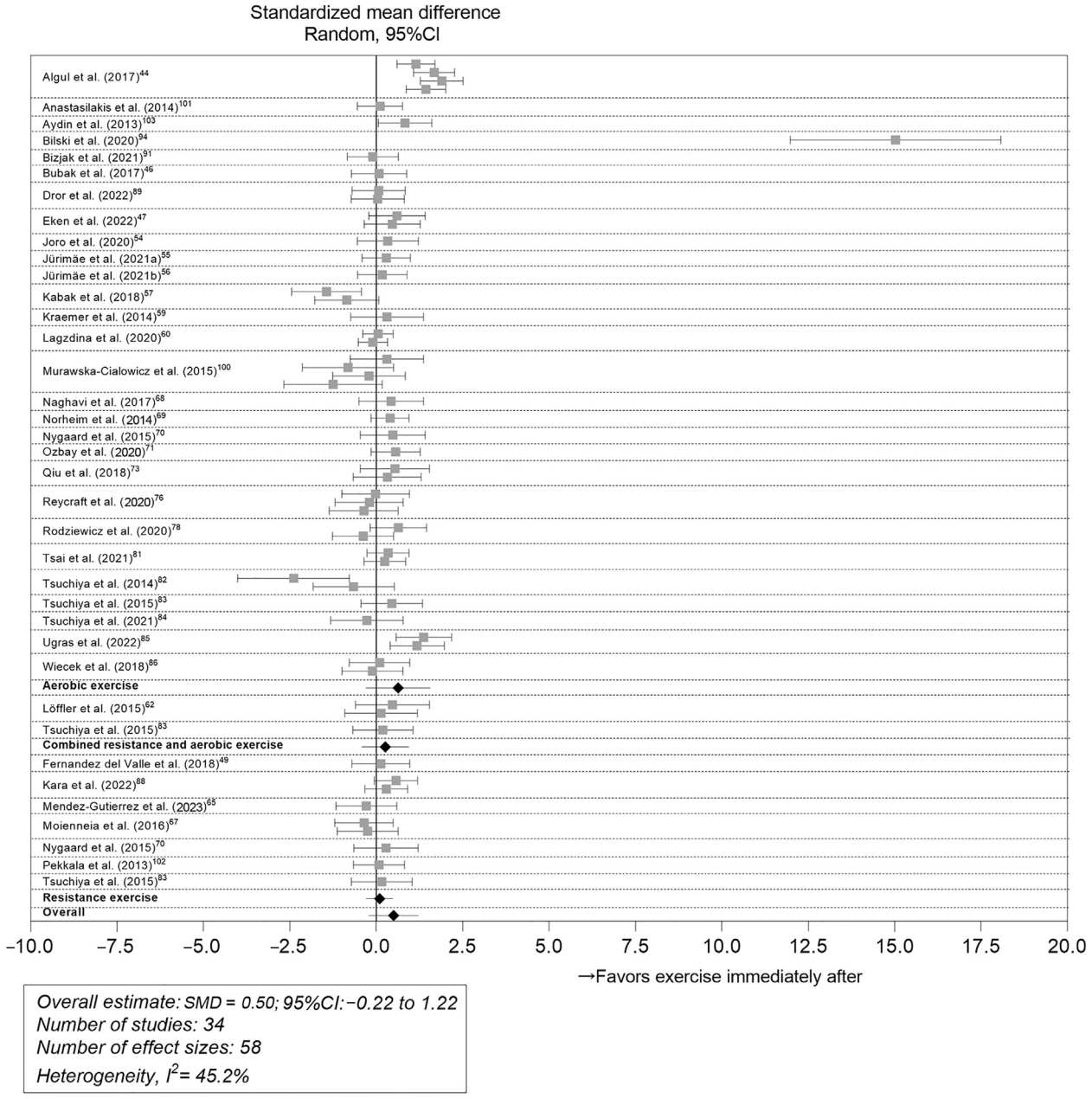

Fig. 3. Forest plot of overall and specific effects on irisin expression immediately following a single bout of exercise. 95%CI = 95% confidence interval; I^2 = heterogeneity test; SMD = standardized mean difference.

3.4. SPARC

3.4.1. Main model effects, sensitivity analysis, and subgroup analysis

3.4.1.1. Main model. Seven studies and 16 effect sizes were undertaken for the SPARC model[50,52,53,75,79,93,104] (Table 3). When examining the main model effect, a non-significant small increase was found (SMD = 0.32; 95%CI: −0.06 to 0.69; $p = 0.08$) and the heterogeneity I^2 was 0%.

3.4.1.2. Immediately after. Seven studies and 9 effect sizes were undertaken for SPARC expression immediately after a single bout of exercise compared to baseline[50,52,53,75,79,93,104] (Table 3 and Fig. 4). When examining the overall effect, a significant small increase was found (SMD = 0.50; 95%CI: 0.01−0.99; $p = 0.05$). For AE a significant moderate increase was found (SMD = 0.66; 95%CI: 0.24−1.07; $p = 0.01$). The other effect sizes were composed by RE from the same study, preventing meta-analysis from being performed.

3.4.1.3. 60 min after. Two studies and 2 effect sizes were undertaken for SPARC expression 60 min after a single bout of exercise compared to baseline[79,93] (Table 3). When examining the overall effect, there was no effect (SMD = −0.04; 95%CI: −0.17 to 0.08; $p = 0.14$). As the studies only included AE, results are the same when subgrouping by exercise mode.

Table 3
Effects of single bouts of exercise on SPARC, OSM, and Decorin expression.

Main model	K	No. of ES	Random-effect meta-analysis			Heterogeneity		
			ES	95%CI	*p*	*Q*	I^2	*p*
SPARC								
Main model effect	7	16	0.32	−0.06 to 0.69	0.08	9.40	0	0.85
Time points								
Immediately after								
Overall effect	7	9	0.50	0.01 to 0.99	0.05	5.10	0	0.75
Aerobic exercise	6	7	0.66	0.24 to 1.07	0.01	1.40	0	0.96
Resistance exercise	NA							
Aerobic + resistance exercise	NA							
60 min								
Overall effect	2	2	−0.04	−0.17 to 0.08	0.14	0	0	0.98
Aerobic exercise	2	2	−0.04	−0.17 to 0.08	0.14	0	0	0.98
Resistance exercise	NA							
Aerobic + resistance exercise	NA							
180 min								
Overall effect	2	2	0.12	−5.30 to 5.54	0.82	0.70	0	0.40
Aerobic exercise	2	2	0.12	−5.30 to 5.54	0.82	0.70	0	0.40
Resistance exercise	NA							
Aerobic + resistance exercise	NA							
24 h								
Overall effect	2	2	−0.26	−6.85 to 6.32	0.70	1.00	0	0.32
Aerobic exercise	2	2	−0.26	−6.85 to 6.32	0.70	1.00	0	0.32
Resistance exercise	NA							
Aerobic + resistance exercise	NA							
OSM								
Main model effect	3	11	0.08	−2.4 to 2.56	0.90	29.60	32.50	0.001
Time points								
Immediately after								
Overall effect	3	7	0.33	−1.23 to 1.88	0.43	3.10	11.00	0.79
Aerobic exercise	3	7	0.33	−1.23 to 1.88	0.43	3.10	11.00	0.79
Resistance exercise	NA							
Aerobic + resistance exercise	NA							
Decorin								
Main model effect	2	13	0.99	−11.14 to 13.12	0.49	21.10	39.00	0.05
Time points								
24 h								
Overall effect	2	5	1.11	−14.04 to 16.26	0.52	13.30	41.90	0.01
Aerobic exercise	NA							
Resistance exercise	2	5	1.11	−14.04 to 16.26	0.52	13.30	41.90	0.01
Aerobic + resistance exercise	NA							

Abbreviations: 95%CI = 95% confidence interval; ES = effect size; I^2 = percentage of variation across studies that is due to heterogeneity; K = number of studies; NA = not available; OSM = oncostatin M; *Q* = Cochran's *Q* test of heterogeneity; SPARC = secreted protein acidic and rich in cysteine.

3.4.1.4. 180 min after. Two studies and 2 effect sizes were undertaken for SPARC expression 180 min after a single bout of exercise compared to baseline[93,104] (Table 3). When examining the overall effect, a non-significant small increase was found (SMD = 0.12; 95%CI: −5.30 to 5.54; $p = 0.82$). As the studies only included AE, results are the same when subgrouping by exercise mode.

3.4.1.5. 24 h after. Two studies and 2 effect sizes were undertaken for SPARC expression 24 h after a single bout of exercise compared to baseline[93,104] (Table 3). When examining the overall effect, a non-significant small decrease was found (SMD = −0.26; 95%CI: −6.85 to 6.32; $p = 0.70$). As the studies only included AE, results are the same when subgrouping by exercise mode.

3.5. OSM

3.5.1. Main model effects, sensitivity analysis, and subgroup analysis

3.5.1.1. Main model. Three studies and 11 effect sizes were undertaken for the OSM model[51–53] (Table 3). When examining the main model effect, a non-significant small increase was found (SMD = 0.08; 95%CI: −2.40 to 2.56; $p = 0.90$) and the heterogeneity I^2 was 32.50%.

3.5.1.2. Immediately after. Three studies and 7 effect sizes were undertaken for OSM expression immediately after a single bout of exercise compared to baseline[51–53] (Table 3 and Fig. 5). When examining the overall effect, a non-significant

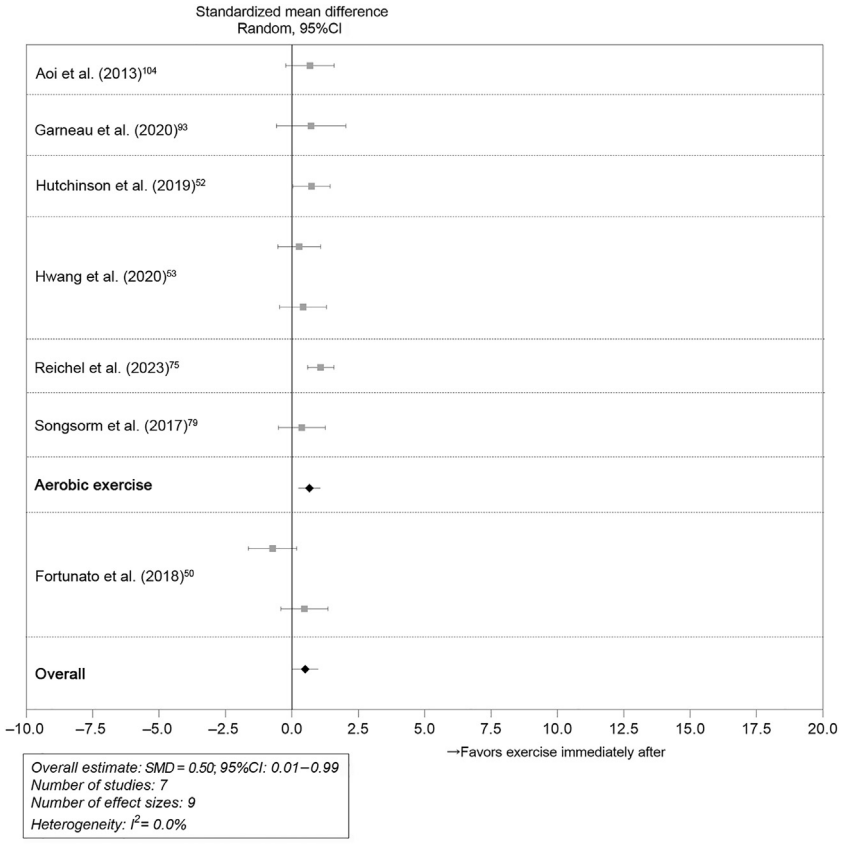

Fig. 4. Forest plot of overall and specific effects on SPARC expression immediately following a single bout of exercise. 95%CI = 95% confidence interval; I^2 = heterogeneity test; SMD = standardized mean difference; SPARC = secreted protein acidic and rich in cysteine.

small increase was found (SMD = 0.33; 95%CI: −1.23 to 1.88; $p = 0.43$). As the studies only included AE, results are the same when subgrouping by exercise mode.

3.6. Decorin

3.6.1. Main model effects, sensitivity analysis, and subgroup analysis

3.6.1.1. Main model. Two studies and 13 effect sizes were undertaken for the decorin model[87,98] (Table 3). When examining the main model effect, a non-significant large increase was found (SMD = 0.99; 95%CI: −11.14 to 13.12; $p = 0.49$) and the heterogeneity I^2 was 39%.

3.6.1.2. 24 h after. Two studies and 5 effect sizes were undertaken for decorin expression 24 h after a single bout of exercise compared to baseline[87,98] (Table 3). When examining the overall effect, a non-significant large increase was found (SMD = 1.11; 95%CI: −14.04 to 16.26; $p = 0.52$). As the studies only included RE, results are the same when subgrouping by exercise mode.

4. Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis examining the overall and specific effects of different exercise modes after a single bout of exercise on the expression of IL-15, irisin, SPARC, OSM, and decorin in healthy adults at different time points post-exercise. There are 3 important findings. First, a single bout of exercise appeared to induce small to large increases in myokine expression, especially when blood was collected immediately after and up to 60 min post-exercise, although due to the large variation in response, the changes were, for the most part, not statistically significant. Second, AE and RE induce alterations in myokine expression with the magnitude of change differing across myokines, although no statistically significant difference was observed between training modes. Third, myokine responses from 180 min to 24 h post-exercise reverted to baseline levels. However, as noted above, most changes were not statistically significant, and so precise conclusions cannot be drawn. Nevertheless, the findings from the current study provide insights into the impact of a single bout of exercise on myokine expression at different time points and emphasize the need for further research to clearly elucidate the effects of a single bout of exercise on myokine response.

4.1. IL-15

Collectively, we examined the exercise effects on IL-15 in healthy individuals and found evidence that a single bout of exercise is likely effective in inducing increases in IL-15 responses from immediately post-exercise up to 24 h post-exercise. However, caution should be taken as some effect sizes showed large variations in 95%CIs, which partially

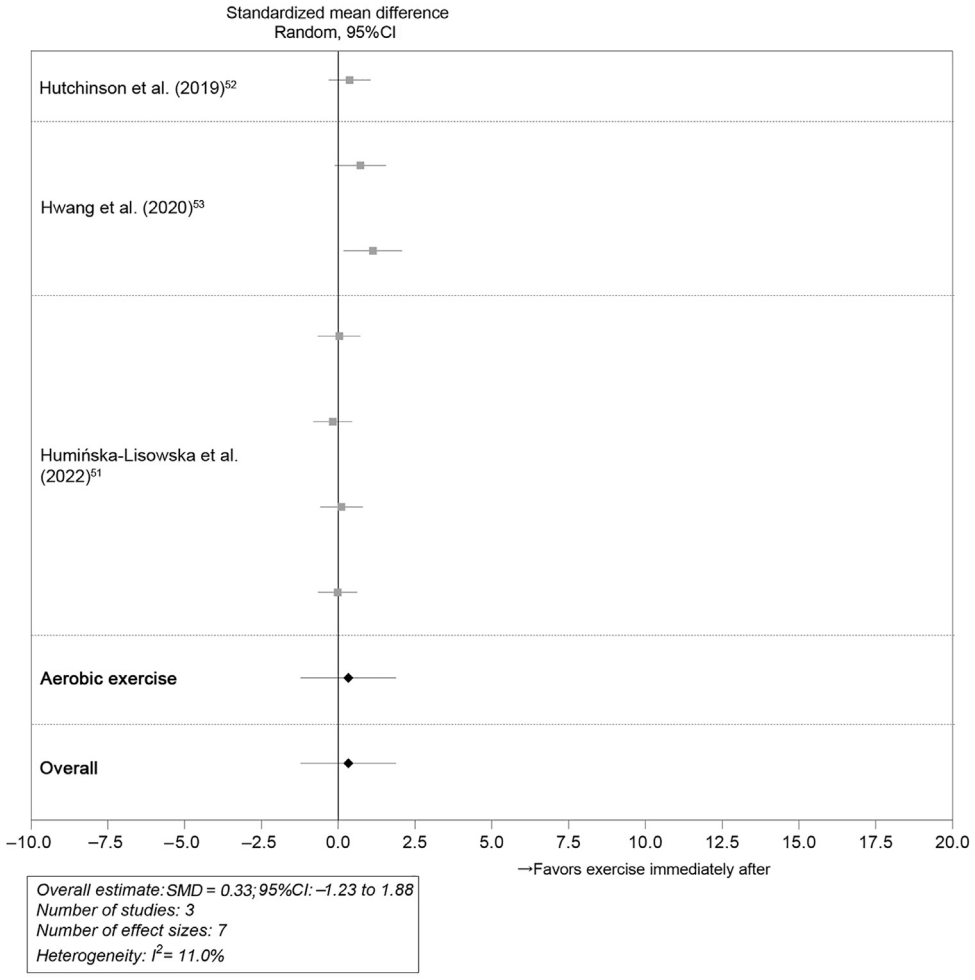

Fig. 5. Forest plot of overall and specific effects on OSM expression immediately following a single bout of exercise. 95%CI = 95% confidence interval; I^2 = heterogeneity test; OSM = oncostatin M; SMD = standardized mean difference.

explains the lack of statistically significant difference as well as the wide response after exercise (Table 1). When data were available, the sub-group analyses revealed that RE appeared to elicit higher IL-15 expression compared to AE, and this was observed immediately after and 60 min post-exercise. The underlying reasons are not readily apparent; however, it should be noted that some studies adopted HIAE with low total volume (i.e., 10 min)[58] while in other studies MICAE lasted only 30 min, which may be below the stimulus threshold to drive substantial changes in IL-15 expression (Supplementary Table 1).[61,64,80] To further support this, He et al.[106] did not report significant differences when comparing a single bout of RE *vs.* HIAE performed for 45−50 min at different time points (i.e., from immediately after up to 72 h post-exercise). Taken together, the volume and intensity adopted for some AE bouts may have skewed the results and, consequently, limited physiological modifications to occur. In contrast, it should be noted that the exercise prescriptions for RE in most of the studies included[45,48,72,98] were in line with the current guidelines,[107] increasing confidence in the findings reported. Additionally, we observed a relatively high heterogeneity (I^2 up to 49.70%), which may have accounted for exercise mode differences. Overall, although no significant differences were observed at any time point, it appears that a single bout of exercise, especially when RE is performed, may represent an exercise mode capable of inducing changes in IL-15 levels at different time points.

4.2. Irisin

It appears that irisin expression increases up to 60 min after a single bout of exercise, which was statistically significant, with a gradual decline to baseline levels over the subsequent 24-h period (Table 2). Although a direct comparison could not be performed and no statistically significant difference was observed, it appears that larger effects were observed when subjects performed a single bout of AE compared to RE, especially up to 60 min post-exercise, even though relatively high heterogeneity was found I^2: 42.70%−46.50%. Interestingly, such differences in irisin levels after AE *vs.* RE were not observed at the other time points. In this regard, it should be acknowledged that the low to moderate intensity (i.e., 40%−60% 1RM) and the number of exercises performed (i.e., only 1 exercise per session) in some RE interventions may have impeded substantial change (Supplementary Table 1).[65,67,88,102] In

contrast, higher volume (i.e., up to 120 min) and intensity (i.e., 60%−80% VO_{2max} or 70% $HR_{reserve}$) performed as MICAE or HIAE likely elicited more substantial increases in irisin.[46,55,56,59,69,70,73,76,81,83,84,89] Furthermore, the number of studies using RE were substantially lower than those using AE; therefore, caution should be taken when comparing these exercise modes for irisin.

Our results are also in line with those of Fox et al.,[29] who found clinically significant increases in irisin expression by 15% immediately after a single bout of exercise without subgrouping by exercise mode. In contrast, our meta-analysis did not reveal statistically significant changes; however, our inclusion criteria differed from the study done by Fox et al.,[29] which included obese subjects with or without metabolic conditions. This may have altered the results as different responses were found when investigating the effects of a single bout of exercise on irisin expression in lean *vs.* obese subjects,[62] highlighting the influence of excessive adipose tissue and low skeletal muscle mass on myokine expression.[93,108] In agreement with our findings, a review by Kazeminasab et al.[31] reported that a single bout of exercise increased irisin expression in healthy individuals (although it was not statistically significant), with AE inducing larger responses compared to RE. However, we examined multiple time points up to 24 h post-exercise, whereas Kazeminasab et al.[31] included blood collected from immediately after up to 54 min after exercise in the same analysis. Such an approach might have introduced potential variations into the outcome, considering the potential of different effects at these time points.[109] Similarly, researchers recently investigated the effects of AE on irisin expression, observing significant increases after a single bout of exercise.[30] However, it should be noted that the authors included cross-over trials with only a 48-h wash-out period.[110] Although evidence is still sparse, it has been assumed that myokines are elevated immediately after exercise followed by a rapid decrease to baseline levels (i.e., from a few hours to more than 24 h).[111] Therefore, including cross-over trials with less than 72 h of total rest may have influenced the results. Taken together, the multiple time point assessments and the robust inclusion criteria in our analysis allow for a more nuanced understanding of irisin expression, enabling insights into the specific response after a single bout of exercise. In summary, although significant differences were few, irisin appears to be elevated by AE up to 60 min after a single bout of exercise.

4.3. SPARC

A single bout of exercise induced significant SPARC elevation immediately post-exercise and a return to initial baseline values thereafter, even though no statistically significant difference was observed at 60 min and 180 min after exercise (Table 3). Interestingly, only 1 study adopting RE was included in our review,[50] which impeded sub-group analysis and the comparison with AE. Regarding AE, most of the studies included had an exercise duration of 30−60 min with intensity from 50% to 70% VO_{2max} or 60% $HR_{reserve}$ using MICAE (Supplementary Table 1),[52,53,75,79,93,104] which appears sufficient to drive alterations in SPARC levels. Furthermore, the very low heterogeneity observed (i.e., $I^2 = 0\%$) increases confidence in the findings. However, given the scarcity of studies, further research is required to explore the impact of different exercise modes at different time intervals on SPARC levels, precluding any additional assumptions about RE at distinct time points. Overall, a single bout of exercise significantly increases SPARC immediately after exercise and returning to baseline levels thereafter.

4.4. OSM

The effects of a single bout of exercise may drive small increases in OSM expression immediately after exercise (Table 3). We report only 3 studies investigating OSM, and as highlighted above for SPARC, they included only AE. There was no statistically significant difference; however, in regard to the exercise prescription for AE, even though the heterogeneity among studies was low (i.e., $I^2 = 11.00\%$), it should be noted that in the study by Humińska-Lisowska et al.[51] subjects performed only a 30-s maximal effort with resistive load on a cycle ergometer (Supplementary Table 1), which may not be sufficient to stimulate OSM responses. Furthermore, no studies have investigated the effects of RE on OSM expression in healthy adults, indicating that future investigations are required. In addition, to detect the changes of OSM in the systemic circulation, more studies collecting blood at different time points are required. In summary, although exercise may have a positive effect on OSM expression, more research is needed to clearly elucidate the effects of different exercise modes at different time points.

4.5. Decorin

When investigating the effects of a single bout of exercise on decorin expression, it appears that large increases can be observed 24 h post-exercise (Table 3). It should be noted that large variations in 95%CIs may have accounted for the lack of statistically significant difference, as was the case for IL-15. As mentioned above with respect to SPARC and OSM, our review included studies performing RE only. In this instance, the training dosage for RE included low- and high-intensity RE (i.e., 50%−80% 1RM, respectively) until volitional failure (Supplementary Table 1).[87] Moreover, Bugera et al.[98] used traditional RE as well as blood flow restriction RE (i.e., 4 sets of 15 to 30 repetitions at 30%−80% 1RM). Although a statistically significant difference was not observed, it should be noted the adoption of an alternative RE method (e.g., blood flow restriction) may guide future investigations of exercise prescriptions to induce myokine changes. However, the relatively high heterogeneity (i.e., $I^2 = 41.90\%$) should be taken into account as well. In summary, due to the paucity of studies, no definitive conclusions can be drawn, highlighting the need for further investigations to comprehensively understand how different exercise modes at different time intervals impact decorin responses.

4.6. Limitations

There are a few limitations in this review which are worthy of comment. First, the population included sedentary, physically active, and trained adult populations. Furthermore, gender, age, and BMI of participants varied among studies, increasing the heterogeneity of this current review. Secondly, there is no consensus about the study design procedures to be adopted when measuring changes in myokine expression before and after a single bout of exercise. Indeed, time of assessment (i.e., a.m. *vs.* p.m.) and difference in hours spent fasting (e.g., 1 h *vs.* 3 h) may have influenced the results.[112] Lastly, there remains a distinct lack of studies investigating myokine expression at different time points, especially 60 min after a single exercise bout.

4.7. Directions for future research

Based on our findings, it appears of utmost importance to investigate the effects of different exercise modes to precisely determine whether or not a single bout of AE or RE drives different responses in myokine expression. It should be noted that there was a paucity of studies investigating RE for SPARC and OSM as well as those examining a single bout of AE for decorin. Additionally, and in line with this suggestion, very few studies explored the effects of a combined approach (i.e., AE + RE) for most of the myokines included. Furthermore, subsequent investigations employing alternative training methods (e.g., blood flow restriction, cluster set, or accentuated eccentric training[113–115]) may shed further light on exercise-induced myokine expression. Since myokines are released in response to muscular contractions and exert their actions on different organs,[6,9–11] targeting of exercise prescription may facilitate clinical implementation of exercise for health, well-being, and disease treatment (e.g., cancer).[12,13] Moreover, blood collection at multiple time points may further elucidate the unique response of myokines to exercise across time. Finally, it is still unknown what are the training parameters to induce substantial myokine responses. Future research should aim to investigate the minimal dosage in terms of volume and/or intensity for both AE and RE, as well as the participant characteristics (e.g., training status) required to drive alterations in myokine expression, therefore elucidating the impact of training parameters on myokine responses.

5. Conclusion

In this systematic review and meta-analysis, we examined the overall and specific effects of a single bout of exercise on myokine expression in healthy adults at different time points post-exercise. It appears that small to large increases can be induced by exercise measured immediately after and up to 60 min following exercise while myokine responses revert toward baseline from 180 min to 24 h post-exercise. Furthermore, both AE and RE induce alterations in myokine expression, although the extent of these changes varies depending on the specific myokines. However, owing to the large variations observed, most of the changes were not statistically significant, indicating that precise conclusions cannot be drawn. Nevertheless, through this research we have expanded our knowledge of the impact of overall effects as well as the effects of different exercise modes on myokine expression. Further research is required to investigate the effects of different exercise modes, volume, and intensity at multiple time points on myokine responses.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions

FB conceived the study design, searched studies in the databases, extracted data, ran statistical analyses, elaborated results, and drafted the manuscript; PL ran statistical analyses; AMM and VN searched studies in the databases and extracted data; DRT, DAG, CB, JSK, and RUN edited and revised the manuscript. All authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

Competing interests

The authors declare that they have no competing interests.

Supplementary materials

Supplementary materials associated with this article can be found in the online version at doi:10.1016/j.jshs.2024.04.005.

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