REVIEW ARTICLE

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Beyond muscles: Investigating immunoregulatory myokines in acute resistance exercise – A systematic review and meta-analysis

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Abstract

Myokines, released from the muscle, enable communication between the working muscles and other tissues. Their release during physical exercise is assumed to depend on immune–hormonal–metabolic interactions concerning mode (endurance or resistance exercise), duration, and intensity. This meta-analysis aims to examine the acute changes of circulating myokines inducing immunoregulatory effects caused by a bout of resistance exercise and to consider potential moderators of the results. Based on this selection strategy, a systematic literature search was conducted for resistance exercise intervention studies measuring interleukin (IL-) 6, IL-10, IL-1ra, tumor necrosis factor (TNF-) α, IL-15, IL-7, transforming growth factor (TGF-) β1, and fractalkines (FKN) before and immediately after resistance exercise in healthy individuals. Random-effects meta-analysis was performed for each myokine. We identified a moderate positive effect of resistance exercise for IL-6 and IL-1ra. Regarding IL-15 and TNF-α, small to moderate effects were found.

Abbreviations: 1RM, one-repetition maximum; AMPK, 5′ adenosine monophosphate-activated protein kinase; APP, acute phase protein; BMI, body mass index; ELISA, enzyme-linked immunosorbent assays; FKN, Fractalkine; g, Hedge's g; IL, interleukin; MD, mean difference; NK cell, natural killer cell; PI, prediction interval; SD, standard deviation; SE, standard error; sFKN, soluble fractalkine; SMD, standard mean difference; TGF, transforming growth factor; Th cell, T helper cell; TNF, tumor necrosis factor.

For IL-10, no significant effect was observed. Due to no data, meta-analyses for IL-7, TGF-β1, and FKN could not be performed. No moderators (training status, type of exercise, risk of bias, age, sex, time of day, exercise volume, exercise intensity, exercise dose) of the results were detected for all tested myokines. Taken together, this systematic review and meta-analysis showed immediate positive effects of an acute resistance exercise session on IL-6, IL-1ra, TNF-α, and IL-15 levels.

KEYWORDS

acute effects, exerkines, immune system, inflammation, myokines, resistance exercise

1 | INTRODUCTION

Cytokines are low-molecular-weight proteins that are involved in multiple processes, including immune regulation, inflammatory reactions, and the maturation of blood cells.[1] Based on the secreting cell or mechanism of action, cytokines have been broadly categorized as chemokines (synthesized to induce leukocyte migration), interleukins (synthesized by leukocytes), lymphokines (synthesized by lymphocytes), adipokines (synthesized by adipocytes), and monokines (synthesized by monocytes and macrophages).[2,3] In the past two decades, multiple studies have shown that muscle cells can also produce a large variety of cytokines.[2,4,5] They are now referred to as myokines.[6-8]

By communicating between the muscle and other organs, including the brain, bone, and vascular system, myokines affect human cognition, mental health, bone formation, and endothelial cell function.[9] Furthermore, it is well established that myokines greatly impact the regulation of immunological processes in response to physical activity.[5,10,11] Released by concentric muscle contractions,[8] they mediate the health-promoting effects of exercise via, for example, activating IL-6-sensitive natural killer (NK) cells,[12] therefore contributing to the protection against diseases associated with low-grade inflammation.[13-15] Given these characteristics, myokines have also been described to belong to the group of exerkines, along with other signaling units that are released in response to exercise.[16,17]

Myokines are not only released by muscle fibers, but also in the regenerating muscle from infiltrating neutrophils and macrophages,[18] fibro-adipogenic progenitors,[19] and satellite cells.[20,21] Thus, if the myokine concentration and not the expression is considered as an outcome parameter, it is not possible to differentiate between muscle-derived and non-muscle-derived cytokines. However, growing evidence from biopsy, gene sequencing, and blood collection studies[7,22,23] suggests that the release of cytokines from working muscle myocytes is far more important than that from immune cells for its systemic increase.

The first cytokine identified as a myokine was the muscle-derived interleukin (IL-) 6 in 2000 by Pedersen's laboratory.[24] Initially, IL-6 was known as a proinflammatory cytokine.[25] Acute trauma or infection causes a local and systemic rise in IL-6, leading to the activation and release of hepatocyte-derived acute phase proteins (APP), such as C-reactive protein.[1,26] This rise in IL-6, APP, and several other cytokines ensures a rapid and targeted immune response.[1]

Following acute exercise, pro- as well as anti-inflammatory pathways are activated via muscle-derived cytokines. Muscle-derived IL-6, in contrast to non-muscle-derived IL-6, exerts anti-inflammatory effects.[27] Its release leads to decreasing levels of tumor necrosis factor (TNF-)α[4,28] or IL-1[1] and increasing concentrations of the anti-inflammatory cytokines IL-1ra and IL-10.[4,23] Their release contributes to an anti-inflammatory environment by inhibiting Th1 cell activity and promoting Th2 cell function, which promotes cellular as well as humoral immunity and inflammatory response.[6,29] Furthermore, immune-related myokines are IL-7,[30] which is, for example, essential for T- and B-cell development,[31,32] and IL-15,[33] which reduces adipose tissue by stimulating lipolysis,[34,35] therefore exerting indirect anti-inflammatory effects by reducing cardiovascular risk factors. Highlighting the complex immunoregulatory processes elicited by an acute exercise bout, post-exercise myokine kinetics are also associated with enhanced leukotaxis and immune cell differentiation for tissue surveillance and regeneration. For instance, TNF-α, activated via transforming growth factor (TGF-)β1, among others, acts as a potential chemotactic factor for neutrophils and monocytes,[36,37] while fractalkines (FKN), either in a cell-surface-bound form or a soluble form (sFKN), promote leukocyte integrin activation as well as facilitate the adhesion of leukocytes to the vascular endothelium and their migration into the tissue.[38]

Existing literature suggests that acute and chronic physical activities are associated with changes in myokine concentrations and their mRNA expression depending on exercise duration, mode, and intensity.[8,39] While there is an extensive body of literature investigating continuous

endurance exercises,[22,40-52] the general cytokine response to intermittent exercise modes has only been scarcely evaluated, and determinants of the response remain comparably poorly studied. This is especially true for resistance exercise, albeit it represents the most direct form of volitional muscle fiber recruitment and an easily implementable exercise form. Yet, even though most findings on the effects of resistance exercise on myokine levels mirror those made in the context of endurance exercise, their magnitudes greatly vary between studies, with some even reporting no changes[46,53,54] or a reduction[55] in myokine concentrations.

To better understand the myokine response to resistance exercise, this systematic review and meta-analysis aims to examine and quantify the acute changes in circulating levels of myokines that have previously been shown to exert relevant immunoregulatory effects induced by a bout of (resistance) exercise and to consider potential moderators of these results. Specifically, IL-6, IL-10, IL-1ra, TNF-α, IL-15, IL-7, TGF-β1, and FKN were reviewed in this analysis. Fostering the understanding of the relationship between exercise modalities and myokine response would, for example, help to predict training outcomes and optimize exercise recommendations for populations with different requirements, such as patients with cancer, multiple sclerosis, or postviral infection syndromes.

2 | METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines[56] were adopted for the literature search and writing process. The PRISMA checklist is provided as a supplementary file. The protocol was pre-registered on PROSPERO (registration number: CRD42022327039, last amendment date: 09/05/22). Literature was searched to examine the acute changes in circulating levels of immunoregulatory myokines (i.e., IL-6, IL-10, IL-1ra, TNF-α, IL-15, IL-7, TGF-β1, and FKN) induced by a bout of resistance exercise. Five different meta-analyses were performed to evaluate blood concentration changes from pre- to immediately post-exercise intervention of (1) IL-6, (2) IL-10, (3) IL-1ra, (4) TNF-α, and (5) IL-15. Due to no data, no analysis could be performed for IL-7, TGF-β1, and FKN which were only considered in the systematic review part of this article.

2.1 | Literature search

The literature search was conducted using databases MEDLINE (via PubMed), Web of Science, Cochrane Library, and SPORTDiscus from November 6, 2023 to

TABLE 1 MeSH terms and search query.

MEDLINE (via PubMed)
Query: (("Resistance Training"[MeSH Terms] OR "resistance exercise"[tiab] OR "resistance training"[tiab] OR "strength training"[tiab] OR "strength exercise"[tiab]) **AND** ("Interleukin-6"[tiab] OR "Interleukine-6"[tiab] OR "IL-6"[tiab] OR "Interleukin-6"[Mesh] OR "Interleukin 1 Receptor Antagonist Protein"[tiab] OR "Interleukin 1 Receptor Antagonist"[tiab] OR "IL-1ra"[tiab] OR "Interleukin1 Receptor Antagonist Protein"[Mesh] OR "Interleukin-10"[tiab] OR "IL-10"[tiab] OR "Interleukin-10"[Mesh] OR "myokine*"[tiab] OR "Interleukin-7"[tiab] OR "IL-7"[tiab] OR "Interleukin-15"[tiab] OR "IL-15"[tiab] OR "Fractalkine"[tiab] OR "CX3CL1"[tiab] OR "tumor necrosis factor"[tiab] OR "tumor necrosis factor"[tiab] OR "tumor-necrosis-factor"[tiab] OR "TNF"[tiab] OR "TGFβ1"[tiab] OR "Transforming growth factor"[tiab] OR "TGF-beta"[tiab])) **NOT** ("infant"[MeSH Terms] OR "child"[MeSH Terms] OR "adolescent"[MeSH Terms] OR "review"[Publication Type] OR "Systematic Review"[Publication Type])
MeSH Terms: Resistance training, Interleukin-6, Interleukin-1 Receptor Antagonist Protein, Interleukin-10, Interleukin-7, Interleukin-15, TNF alpha, Fractalkine, Transforming Growth Factor

December 13, 2023. The search query was created based on MeSH terms and related vocabulary covering the main domains of resistance exercise and interleukins (see Table 1). Additionally, the reference lists of the included studies were screened.

2.2 | Eligibility criteria

Eligibility criteria were determined using a PICOS (participants, interventions, comparison, outcomes, study design) approach.

1. Participants: Healthy participants between 18 and 60 years were included in the review. Studies examining participants older than 60 years were excluded. Individuals suffering from any disease or injury (chronic or acute) were excluded from the review as well.
2. Interventions: All studies comprising a single resistance exercise session defined as concentric or eccentric muscle actions overcoming externally applied resistance were included in the review. If a study included an exercise program, but an acute measurement was conducted before and after a single resistance training session, this acute intervention was included in this review. Studies combining resistance training with endurance exercise, conducting an exercise program over several weeks, or combining exercise with additional treatments possibly altering the physiological response to exercise were

excluded from the review. In addition, studies including interventions such as yoga, stretching, breathing exercises, or other types of exercise that do not fit the definition of resistance exercise were excluded from the review. When studies had multiple interventions, only the intervention groups assessing the effect of resistance exercise were included in the review.

3. Comparison: To be considered, the study's outcome parameters must have been measured pre-exercise and immediately post-exercise. Studies with no baseline or follow-up measurements later than 5 min post-exercise were excluded from the review.

4. Outcomes: Studies assessing the changes in blood serum or plasma concentration of either IL-6, IL-10, IL-1ra, TNF-α, IL-15, IL-7, TGF-β1, or FKN were included in the review.

5. Study design: Randomized and non-randomized clinical trials published in English or German in a peer-reviewed journal. Case studies, animal studies, reviews, cross-sectional or retrospective studies, and longitudinal study designs were excluded from the review.

2.3 | Study selection

The studies found in the literature databases were uploaded to Rayyan (https://www.rayyan.ai/), a free platform allowing the authors to screen the records independently and blinded to the decisions of others. MR and SH made the study selection. First, duplicates were removed. Thereafter, titles and abstracts were screened, and studies not fitting the eligibility criteria were excluded. Disagreements between the reviewers after either the screening of titles and abstracts or full-text screening were solved by discussion. Figure 1 outlines the selection process.

2.4 | Data extraction

Data extraction was conducted by MR. First, general information like authors, study design, and sample size were extracted from the studies. Second, for each intervention group, myokine levels (pre- and immediately post-intervention) with mean and standard deviation (or standard error of the mean or 95% confidence interval) were extracted. Third, participant characteristics such as sex, age, height, weight, and body mass index (BMI) were extracted. Fourth, the resistance training status was also collected. Participants were considered inexperienced if they were described as untrained or sedentary or did not participate in any kind of regular resistance training 6 months before testing. Moreover, the resistance exercises, training parameters (number of sets and
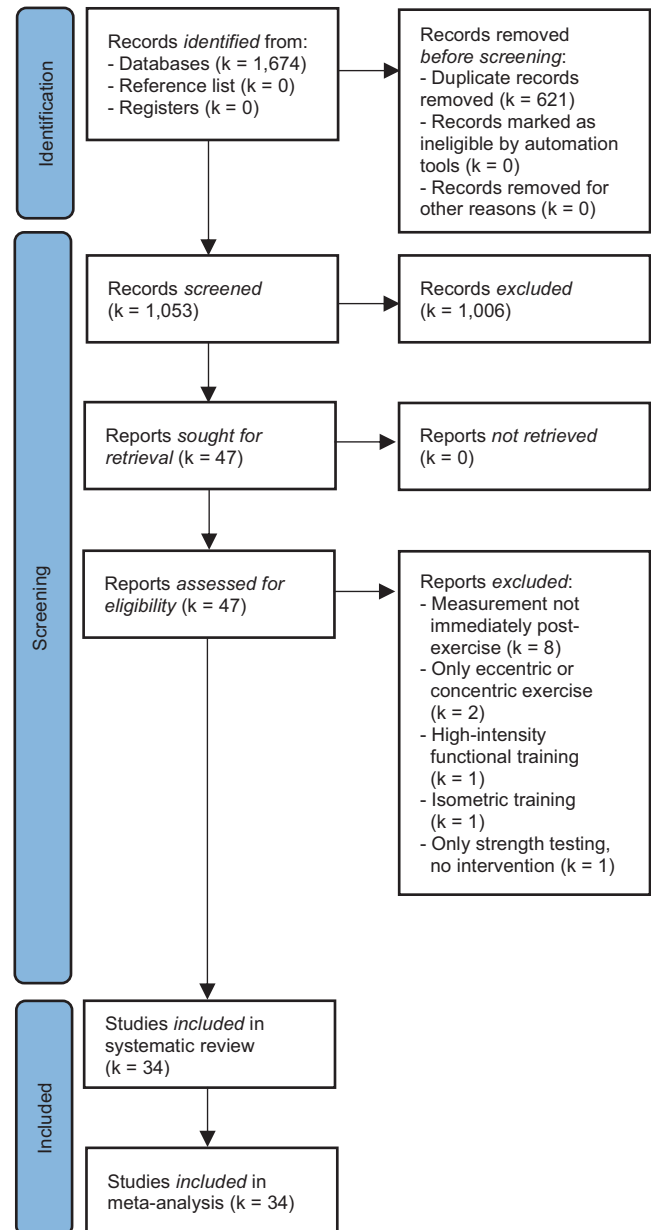
FIGURE 1 Flowchart of literature search and study selection.

repetitions, intra- and interset rest), and intensity were extracted. Furthermore, we computed the dose as the product of intensity and volume, as adopted by Herold et al.[57] The exercise intensity is mostly provided as one-repetition maximum (1RM) or multiple-repetition maximum. Since only the 1RM is considered for calculating the dose, the multiple-repetition maximum is, based on Bächle and Earle,[58] converted to the 1RM if this is the only one reported in the studies. Finally, the time of the day and the type of sample gathered were recorded.

If the authors did not provide exact values, the WebPlotDigitizer digitization program (https://automeris.io/WebPlotDigitizer/) was used to extract plotted data. In parallel, corresponding authors were contacted to retrieve missing data.

2.5 | Risk of bias assessment

The risk of bias in individual studies was assessed using the ROBINS-1 tool.[59] As it evaluates the quality of studies performing a controlled pre- and post-study intervention, this tool is the most suitable quality assessment for this review. The ROBINS-1 tool consists of seven domains appraising the risk of bias. In the case of this review, the domain "bias due to deviations from intended interventions" was not considered since a comparison with a control group is not necessary. Every domain was evaluated via signal questions that were derived from Palmowski et al.[60] Based on this, the individual domains were classified as having either a low, moderate, serious, or critical risk of bias or no information available on which the judgment could be based. Overall, a study was judged to be at low risk of bias if all domains were assessed to be at low risk of bias and moderate risk when at least one domain shows a moderate risk of bias. A serious risk of bias was present when the study was ranked at serious risk in at least one domain but not at critical risk in any domain. With at least one domain at critical risk of bias, the overall study was judged to be at critical risk of bias. No judgment was possible if there was no clear indication that the study was at serious or critical risk of bias and a lack of information was found in one or more key domains. The assessment of the risk of bias was done independently by MR and SH. The interrater coefficient of correlation of the overall judgment of the risk of bias was $r = .81$. Any disagreements were then solved by discussion.

2.6 | Effect sizes

Changes in myokine concentrations were converted to standardized mean differences, calculated as Hedges′ g (g) to account for small-study sample sizes. All studies had within-subject designs with pre- and post-intervention values. All effects had the same direction, and a positive effect size denotes an increase in those five myokines after the exercise intervention. By convention, Hedges′ g values of 0.2, 0.5, and 0.8 are, respectively, considered small, moderate, and large.

The Hedges′ g (SMD = MD/SDpooled) and its standard error were computed according to the recommendations from Borenstein et al.[61] (4.15 – page 24) and the Cochrane Handbook (chapter 23, section 23.2.7.2). The standard error was computed using the imputation of a correlation coefficient at .70 (chosen based on literature and available data) between the immune values pre- and postintervention. To assess the reliability of this coefficient, sensitivity analyses were run ±.15 the chosen coefficient (between .55 and .85–.05 per interval). Several minor differences in

influential outlier detection, trim-and-fill analysis, and moderator analysis were detected. For clarity, those differences will be mentioned in the Results section.

2.7 | Statistical analysis

All analyses were conducted using R Studio (v1.4.1106), using the packages meta, metafor, and metaviz.[62] The full R script and all CSV files used for analyses (including the ones of the sensitivity analysis) are available on the Open Science Framework (doi: 10.17605/OSF.IO/5JKFA). Effect sizes across studies were pooled using a random-effect model.[63] Separate meta-analyses were run for each myokine of interest (i.e., IL-6, IL-10, IL-1ra, TNF-α, IL-15). According to Viechtbauer and Cheung,[62] influential outliers were estimated using studentized deleted residuals and DFBETAS. An outcome was considered as being an outlier if its studentized residual was greater than three in absolute magnitude. It called for closer inspection if its studentized residual was greater than 1.96 in absolute magnitude. The DFBETAS was computed to evaluate if these outliers should also be considered influential cases. According to Viechtbauer and Cheung,[62] DFBETAS greater than one is often considered as being an influential case when considering small to medium datasets.

2.8 | Heterogeneity

The between-study heterogeneity was measured using τ^2 (variance of the true effect), using Hedges′ estimator,[64] and further assessed using the I^2 statistic (measures the percentage of the observed variance reflecting the variance of the true effect rather than sampling error).[65,66] The prediction interval (PI) was also computed to consider the potential effect of an exercise bout on myokine levels when applied within an individual study setting, as this may differ from the average effect.[67] The Hartung and Knapp method was used to adjust confidence intervals and test statistics.[68-70]

Moderator analyses were planned for age, sex, training status, exercise type, exercise volume, exercise intensity, exercise dose, time of the day, and estimated risk of bias. Subgroup analyses were performed for categorical moderators (i.e., sex, training status, exercise type, time of the day, and risk of bias estimated), and meta-regressions were performed for continuous moderators (i.e., age, exercise volume, intensity, and dose). Multivariate moderator analyses were performed to assess the combined effects of different and non-overlapping exercise modalities (i.e., only exercise dose was used among intensity, volume, and dose) using the metafor package (rma function). When possible,

the interactions between exercise dose and training status as well as between exercise dose and exercise types were added to this multiple regression model.

2.9 | Small-study effects

Small-study effects (an indicator of potential publication bias) were first assessed by visual inspection of the funnel plots and further assessed using Egger's test (significant when $p < .100$, one-tailed). If evidence of asymmetry was found, the trim-and-fill procedure was used to estimate the number of potentially missing effects and to provide an adjusted Hedges' g estimate.[62,71,72]

3 | RESULTS

3.1 | Study selection

In total, 1674 studies were found through a systematic literature search in these four databases: PubMed (665), Web of Science (576), Cochrane Library (293), and SPORTDiscus.[73] After removing duplicates, 1053 titles and abstracts were screened for eligibility. As a result, 47 reports were sought for retrieval and were assessed for eligibility. A total of 34 studies were included in the systematic review and meta-analyses (Figure 1).

3.2 | Study characteristics

Thirty-four studies, including 64 intervention groups with a total of 495 participants (89% male/11% female), were included in this systematic review and meta-analysis. From the total of 34 studies included in the meta-analyses, 29 studies investigated IL-6 with 56 effect sizes,[55,74-100] 11 examined IL-10 with 24 effect sizes,[55,74,75,77-80,85,88,89,97] and further 5 analyzed IL-1ra with 14 effect sizes.[77,83-85,97] Nine studies with 15 effect sizes looked into TNF-α,[75,78,87,89,96,98,101-103] and five studies accounting for eight effect sizes investigated IL-15.[33,88,91,104,105] As displayed in Table 2, only two studies investigated the effects of resistance exercise on female participants,[88,97] and two studies had at least one female intervention group investing sex-dependent differences in results.[74,99] One study did not report their participants' sex.[100] Participants were, on average, 24.7 (18–51) years old and had a mean BMI of 24.71 kg/m². Sixty-four percent of the participants were described as experienced in resistance training, whereas 36% had no resistance training experience. Regarding the single exercise session, 42% of the participants underwent a full-body exercise session, whereas 50% of the interventions

comprised a lower body workout and 8% an upper body resistance training. Session volume (sets × repetitions) ranged from 15 to 345 repetitions, and exercise intensity from 30% to 100% of the 1RM. More than half of the studies did not report their testing time (36 out of 64 intervention groups), yet among the reported ones, the majority of the sessions were conducted in the morning. Seventy-two percent of the studies used enzyme-linked immunosorbent assays (ELISA) to analyze their blood samples. All study characteristics are displayed in detail in Table 2.

3.3 | Risk of bias assessment

Only one study was deemed to be at low risk of bias (3%), whereas 12 were labeled as moderate (35%). Eleven studies were assessed to be at serious risk of bias (32%), and another 10 showed a critical risk of bias (30%). If one study was considered to be at serious or critical risk of bias, most inconsistencies occurred in the first, the confounding domain. Less than half of the studies showed a low or moderate risk of bias (47%) in that domain. The main reasons for the poor ratings in this domain were the lack of control of nutritional intake, no indication of 24 to 48 h of rest before the intervention, or differing warm-ups between the participants. Detailed results are shown in Table 3. As more than half of the studies demonstrated a serious to critical risk of bias (62%), the overall quality of the existing literature can be depicted as insufficient.

The results of the five meta-analyses performed, respectively, for IL-6, IL-10, IL-1ra, TNF-α, and IL-15 are presented next and summarized in Table 4.

3.4 | Interleukin-6

3.4.1 | Main analysis

The average effect size for IL-6 was moderate ($k = 56$, $g = 0.45$, $p < .001$), and its confidence interval was between 0.29 and 0.61, which indicates that in a universe of comparable studies to the one included in this analysis, the mean effect size could fall anywhere in between small and moderate (Figure S1). This range did not include 0, revealing that the true effect is likely positive. The heterogeneity was large (PI [−0.74; 1.65], $\tau^2 = 0.35$), with a large part representing the variance of the true effect ($I^2 = 75.6\%$). According to the PI, in the universe of populations represented by the included studies, the true effect, in 95% of cases, will fall between moderate negative and very large positive effects. No influential outliers were detected. There was a small visual asymmetry (Figure 2A), confirmed by Egger's test

(intercept $=-0.84$, $p<.001$), but no adjustments were necessary according to the trim-and-fill analysis ($SE=4.12$).

3.4.2 | Moderator analysis (categorical)

Sex
The sex distribution was skewed, with most studies analyzing male participants. Male ($k=46$, $g=0.43$, 95% CI 0.28; 0.59), female ($k=6$, $g=0.34$, 95% CI -0.22; 0.91), and mixed ($k=2$, $g=0.13$, 95% CI -0.86; 1.13) groups of participants significantly differ ($Q_M=7.52$, $df=2$, $p<.050$). Nevertheless, the "mixed" category only had two effects relying on the same study. No differences were detected when only male and female participants were compared ($Q_M=0.16$, $df=1$, $p=.693$).

Training status
Samples experienced ($k=34$, $g=0.49$, 95% CI 0.24; 0.74) and inexperienced with resistance training ($k=22$, $g=0.39$, 95% CI 0.21; 0.57) did not differ significantly ($Q_M=0.47$, $df=1$, $p=.493$).

Type of exercise
Full-body ($k=26$, $g=0.56$, 95% CI 0.26; 0.87), lower body ($k=25$, $g=0.41$, 95% CI 0.22; 0.61), and upper body exercise trainings ($k=5$, $g=0.17$, 95% CI -0.14; 0.48) were not significantly different ($Q_M=5.04$, $df=2$, $p=.081$). One can note that during the sensitivity analysis, exercise type reached significance when using a correlation coefficient of .85 (see section 2.6).

Time of the day
The testing moment was not reported for 68.9% of the effects; thus, this analysis may not represent the full set of studies included in this manuscript. Testing times in the morning ($k=17$, $g=0.32$, 95% CI 0.05; 0.59) and in the afternoon ($k=6$, $g=0.07$, 95% CI -0.12; 0.27) did not differ significantly ($Q_M=2.67$, $df=1$, $p=.103$).

Risk of bias
The four categories of the risk of bias assessment, low ($k=2$, $g=0.16$, 95% CI -1.36; 1.68), moderate ($k=20$, $g=0.39$, 95% CI 0.07; 0.70), serious ($k=16$, $g=0.39$, 95% CI 0.15; 0.62), and critical ($k=18$, $g=0.64$, 95% CI 0.30; 0.97) risk of bias were not significantly different ($Q_M=5.96$, $df=3$, $p=.113$).

3.4.3 | Moderator analysis (continuous)

Age
Meta-regression revealed that the age of participants was not a significant moderator of the immediate IL-6 response to exercise ($k=56$, $R^2=0\%$, $p=.409$). It must be considered that the meta-regression was based on mean age values and did not necessarily represent the sample homogeneously.

Exercise volume
Meta-regression revealed that the exercise volume was not a significant moderator of the immediate IL-6 response to exercise ($k=56$, $R^2=0\%$, $p=.789$).

Exercise intensity
The exercise intensity was not reported in two studies with four effect sizes.[76,81] Subsequently, these studies were withdrawn from the analysis. Meta-regression revealed that the exercise intensity was not a significant moderator of the immediate IL-6 response to exercise ($k=52$, $R^2=0\%$, $p=.300$).

Exercise dose
The exercise dose was not computed in two studies with four effect sizes.[76,81] Subsequently, these studies were withdrawn from the analysis. Meta-regression revealed that the exercise dose was not a significant moderator of the immediate IL-6 response to exercise ($k=52$, $R^2=0\%$, $p=.769$).

3.4.4 | Moderator analysis (multivariate)

Time of the day was not considered in the multivariate analysis to avoid losing all studies not reporting this information. The model considered in the multivariate analysis (including sex, training status, exercise dose, exercise type, age, training status × exercise dose, exercise type × exercise dose) was not significant (coeff. 2:11; $F(10, 40)=1.274$, $p=.277$, $R^2=6.91\%$).

3.5 | Interleukin-10

3.5.1 | Main analysis

The average effect size for IL-10 was small ($k=24$, $g=0.14$, $p=.221$), and its confidence interval was between -0.09 and 0.36, which indicates that in a universe of comparable studies to the one included in this analysis, the mean effect size could fall anywhere in between very small negative and small to moderate positive (Figure S2). The heterogeneity was large (PI [-0.93; 1.20], $\tau^2=0.25$), with a large part representing the variance of the true effect ($I^2=73.8\%$). According to the PI, in the universe of populations represented by the included studies, the true effect in 95% of cases will fall between large negative and large positive effects. No influential outliers were detected. A potential small visual asymmetry was assumed (Figure 2E) and

TABLE 2 Characteristics of the studies included in the systematic review and meta-analysis.

Reference	Design	N (m/f)	Age (years), $M \pm SD$	BMI (kg/m²), $M \pm SD$	Resistance training status	Exercises
Agostinete et al.[77]	Randomized cross-over	8 (8/0)	23.5 ± 3.1	24.7 ± NR	Inexperienced	Squat, bench press, T-barrow
	Randomized cross-over	8 (8/0)	23.5 ± 3.1	24.7 ± NR	Inexperienced	Squat, bench press, T-barrow
	Randomized cross-over	8 (8/0)	23.5 ± 3.1	24.7 ± NR	Inexperienced	Squat, bench press, T-barrow
Barquilha et al.[100]	Pre–Post	16 (NR)	21 ± 2	NR	Inexperienced	Bench press, shoulder press, parallel squat, leg curl, and lat pull down
Benini et al.[74]	Pre–Post	7 (7/0)	27.5 ± 1.2	25.1 ± NR	Experienced	Back squat, leg extension, leg curl, seated row, lat pull down, bench press, pec deck, biceps curl, triceps pulley, calf raise
	Pre–Post	7 (0/7)	24.4 ± 0.9	22.9 ± NR	Experienced	Back squat, leg extension, leg curl, seated row, lat pull down, bench press, pec deck, biceps curl, triceps pulley, calf raise
Brenner et al.[78]	Randomized cross-over	8 (8/0)	24.9 ± 2.3	24.8 ± NR	Inexperienced	Biceps curl, knee extension, hamstrings curl, bench press, leg press
Bugera et al.[105]	Randomized cross-over	10 (10/0)	25.78 ± 3.56	25.93 ± 2.22	Experienced	Knee extension
	Randomized cross-over	10 (10/0)	25.78 ± 3.56	25.93 ± 2.22	Experienced	Knee extension
Cui et al.[79]	Pre–Post	15 (15/0)	19.36 ± 0.14	21.30 ± 0.25	Inexperienced	Bench press, squat, pull down, overhead press, standing dumbbell curl
	Pre–Post	15 (15/0)	19.72 ± 0.2	22.12 ± 0.31	Inexperienced	Bench press, squat, pull down, overhead press, standing dumbbell curl
	Pre–Post	15 (15/0)	18.87 ± 0.12	21.90 ± 0.30	Inexperienced	Bench press, squat, pull down, overhead press, standing dumbbell curl
Fatouros et al.[80]	Pre–Post	17 (17/0)	23.8 ± 1.2	27.5 ± 0.5	Inexperienced	Chest press, seated row, leg press, shoulder press, leg extension, leg curls, arm curls, triceps extension, abdominal curls, lower back extensions
Gadruni et al.[81]	Pre–Post	7 (7/0)	22.43 ± 1.71	20.13 ± 1.09	Experienced	Hip flexion, − extension, − abduction with band
	Pre–Post	7 (7/0)	22.86 ± 1.34	24.85 ± 0.81	Inexperienced	Hip flexion, − extension, − abduction with band
Gerosa-Neto et al.[75]	Randomized cross-over	8 (8/0)	25.2 ± 4.1	24 ± NR	Experienced	Squats, bench press
	Randomized cross-over	8 (8/0)	25.2 ± 4.1	24 ± NR	Experienced	Squats, bench press

Volume sets × reps; rest (min); Con: Ecc (s)	Intensity	Dose (volume × intensity)	Time of day	Analysis method	Myokines	Hedges' g
(3 × 4) × until movement failure; 0.5	70% of 1 RM	5740	NR	ELISA	IL-1ra, IL-6, IL-10	↑↑↑, ↑↑, ↑↑↑
(3 × 4) × until movement failure; 1.5	70% of 1 RM	7630	NR	ELISA	IL-1ra, IL-6, IL-10	↑, ↑, ↑↑↑
(3 × 4) × reps equal to second condition with 1.5 s rest; 0.5	70% of 1 RM	7630	NR	ELISA	IL-1ra, IL-6, IL-10	↑, ↑↑, ↑↑↑
(5 × 3) × 10; 1	10 RM	9000	NR	ELISA	IL-6	↑↑↑
(10 × 3) × 8–10; 1.5–2	8–10 RM	20 790	NR	ELISA	IL-6, IL-10	↑↑↑, ↑↑
(10 × 3) × 8–10; 1.5–2	8–10 RM	20 790	NR	ELISA	IL-6, IL-10	↑, ↓
(5 × 3) × 10; NR	60–70% of 1 RM	9750	NR	ELISA	IL-6, IL-10, TNF-α	↑, ↓↓, ↑
75; 0.5	30% of 1 RM	2250	NR	ELISA	IL-6, IL-15	ND, =
4 × 7; 1	80% of 1 RM	2240	NR	ELISA	IL-6, IL-15	ND, =
(5 × 3) × 16–30; 1	40% of 1 RM	13 800	16:00	ECLIA (IL-6), RIA (IL-10)	IL-6, IL-10	↓, ↑
(5 × 3) × 12; 2	70% of 1 RM	12 600	16:00	ECLIA (IL-6), RIA (IL-10)	IL-6, IL-10	↑, ↓
(5 × 4) × 6; 3	90% of 1 RM	10 800	16:00	ECLIA (IL-6), RIA (IL-10)	IL-6, IL-10	↑, ↓
(10 × 10) × 3; 0.5	70–75% of 1 RM	23 925	NR	Biochip Array Technology	IL-6, IL-10	↑, ↑
(3 × 3) × 10; 3, 5 (when exercises changed)	2.2 m band, decreased by 10 cm each set	NR	NR	ELISA	IL-6	↑↑
(3 × 3) × 10; 3, 5 (when exercises changed)	2.2 m band, decreased by 10 cm each set	NR	NR	ELISA	IL-6	↑↑↑
(2 × 8) × until exhaustion; 0.5	90% of 1 RM	2520	NR	ELISA	IL-6, IL-10, TNF-α	↑↑↑, =, ↑↑↑
(2 × 8) × until exhaustion; 1.5	90% of 1 RM	4140	NR	ELISA	IL-6, IL-10, TNF-α	↓, ↓, ↑↑

(Continues)

TABLE 2 (Continued)

Reference	Design	N (m/f)	Age (years), $M \pm SD$	BMI (kg/m²), $M \pm SD$	Resistance training status	Exercises
Gordon et al.[76]	Pre–Post	9 (9/0)	21.8 ± 2.0	28.4 ± NR	Experienced	Isokinetic concentric knee extension and eccentric knee flexion at 60°/s
	Pre–Post	10 (10/0)	47.0 ± 4.4	31 ± NR	Experienced	Isokinetic concentric knee extension and eccentric knee flexion at 60°/s
Goto et al.[82]	Randomized cross-over	10 (10/0)	23 ± 1	23.7 ± NR	Experienced	Chest press, lat pull down, leg press, knee extension, seated rowing, shoulder press, arm curl, triceps press down
He et al.[104]	Randomized cross-over	17 (17/0)	23 ± 2	22 ± 2	Inexperienced	Back squat, bench press, barbell deadlift, barbell row, barbell military press, standing biceps curl, sit-ups
Heavens et al.[99]	Pre–Post	9 (9/0)	23.6 ± 3.5	26 ± NR	Experienced	Back squat, bench press, deadlift
	Pre–Post	9 (0/9)	22.9 ± 2	24.1 ± NR	Experienced	Back squat, bench press, deadlift
Ihalainen et al.[84]	Randomized cross-over	12 (12/0)	28.2 ± 3.5	24.6 ± NR	Inexperienced	Leg press
	Randomized cross-over	12 (12/0)	28.2 ± 3.5	24.6 ± NR	Inexperienced	Leg press
Ihalainen et al.[83]	Randomized cross-over	8 (8/0)	31.0 ± 0.9	26.8 ± 1.37	Inexperienced	Leg press
	Randomized cross-over	8 (8/0)	31.0 ± 0.9	26.8 ± 1.37	Inexperienced	Leg press
	Randomized cross-over	8 (8/0)	31.0 ± 0.9	26.6 ± 1.24	Experienced	Leg press
	Randomized cross-over	8 (8/0)	31.0 ± 0.9	26.6 ± 1.24	Experienced	Leg press
Izquierdo et al.[85]	Pre–Post	12 (12/0)	33 ± 4.4	23.5 ± NR	Inexperienced	Leg press
	Pre–Post	12 (12/0)	33 ± 4.4	23.5 ± NR	Experienced	Leg press
	Pre–Post	12 (12/0)	33 ± 4.4	23.5 ± NR	Experienced	Leg press
Joisten et al.[86]	Randomized cross-over	24 (24/0)	24.6 ± 3.9	25.4 ± 2.7	Inexperienced	Chest press, lat pull, leg curl, leg extension, back extension
Krüger et al.[87]	Cross-over	15 (15/0)	26.8 ± 1.01	24.33 ± 0.79	Inexperienced	Bench press, latissimus pull downs, seated rows, shoulder press, leg press, shoulder pull downs, biceps curls, leg curls
	Cross-over	15 (15/0)	26.8 ± 1.01	24.33 ± 0.79	Inexperienced	Bench press, latissimus pull downs, seated rows, shoulder press, leg press, shoulder pull downs, biceps curls, leg curls
Lipford et al.[103]	Pre–Post	10 (7/3)	26.3 ± 7.15	23.1 ± 4.51	Inexperienced	Knee extension, knee flexion

Volume sets × reps; rest (min); Con: Ecc (s)	Intensity	Dose (volume × intensity)	Time of day	Analysis method	Myokines	Hedges' g
8 × 10; 1	Maximum voluntary effort	NR	NR	High-sensitivity multiplex assay	IL-6	↑↑↑
8 × 10; 1	Maximum voluntary effort	NR	NR	High-sensitivity multiplex assay	IL-6	=
(2 × 4) × 12, (6 × 3) × 12; 2	65% of 1 RM	6240	08:00	ELISA	IL-6	↑↑↑
(7 × 4) × 8–10; 1–1.5	70–75% of 1RM	18 270	Morning	ELISA	IL-15	↑↑↑
(3 × 10) × 10–1 (descending each set by 1 rep.); as short as possible	75% of 1 RM	12 375	Morning	ELISA	IL-6	↑↑↑
(3 × 10) × 10–1 (descending each set by 1 rep.); as short as possible	75% of 1 RM	12 375	Morning	ELISA	IL-6	↑↑↑
15 × 1; 3	100% of 1 RM	1500	NR	ELISA	IL-1ra, IL-6	↑↑↑, ↑↑
5 × 10; 2	80% of 1 RM	4000	NR	ELISA	IL-1ra, IL-6	↑↑↑, ↑↑
5 × 10; 2	80% of 1 RM	4000	NR	ELISA	IL-1ra, IL-6	↑↑, ↑↑↑
10 × 5; 3	60% of 1 RM	3000	NR	ELISA	IL-1ra, IL-6	↑↑, ↑↑↑
5 × 10; 2	80% of 1 RM	4000	NR	ELISA	IL-1ra, IL-6	↑↑↑, ↑↑
10 × 5; 3	60% of 1 RM	3000	NR	ELISA	IL-1ra, IL-6	↑↑↑, ↑↑
5 × 10; 2	10 RM	4200	NR	ELISA	IL-1ra, IL-6, IL-10	↑, =, =
5 × 10; 2	10 RM	4200	NR	ELISA	IL-1ra, IL-6, IL-10	↑↑↑, ↑, ↓
5 × 10; 2	10 RM from beginning	3400	NR	ELISA	IL-1ra, IL-6, IL-10	↑↑↑, ↑, ↑↑
(5 × 4) × 8–10; 1	70% of 1 RM	12 600	8:00–11:00	ELISA	IL-6	↑
8 × Reps equal to second condition; 2–3	60% of 1 RM	5160	08:30	ELISA	IL-6, TNF-α	=, ↑↑
8 × until exhaustion; 2–3	75% of 1 RM	6450	08:30	ELISA	IL-6, TNF-α	↑, ↑
(2 × 4) × 8; 1	85% of 1 RM	5440	6:00–8:00	ELISA	TNF-α	↓

(Continues)

TABLE 2 (Continued)

Reference	Design	N (m/f)	Age (years), $M \pm SD$	BMI (kg/m^2), $M \pm SD$	Resistance training status	Exercises
Lira et al.[55]	Randomized cross-over	12 (12/0)	25.3 ± 5.9	24.5 ± NR	Experienced	45° leg press, leg extension, leg curl, bench press, T-bar row, and elbow curl
	Randomized cross-over	12 (12/0)	25.3 ± 5.9	24.5 ± NR	Experienced	45° leg press, leg extension, and leg curl
	Randomized cross-over	12 (12/0)	25.3 ± 5.9	24.5 ± NR	Experienced	Bench press, T-bar row, elbow curl
Luk et al.[88]	Randomized cross-over	13 (0/13)	24 ± 4	25.0 ± 3.2	Experienced	Back squat
	Randomized cross-over	13 (0/13)	24 ± 4	25.0 ± 3.2	Experienced	Back squat
Marucci-Barbosa et al.[89]	Cross-over	12 (12/0)	25.2 ± 3.01	25.15 ± 1.76	Experienced	Leg press 45°, leg curl, leg extension
	Cross-over	12 (12/0)	25.2 ± 3.01	25.15 ± 1.76	Experienced	Leg press 45°, leg curl, leg extension
Nakajima et al.[90]	Randomized cross-over	9 (9/0)	41 ± 3	24 ± 2	Inexperienced	Leg press, leg extension, leg curl
Notbohm et al.[97]	Pre–Post	13 (0/13)	24 ± 4	22.4 ± 2.6	Experienced	Back squat
	Pre–Post	8 (0/8)	22 ± 3	21.5 ± 1.8	Experienced	Back squat
Oliver et al.[91]	Randomized cross-over	10 (10/0)	27 ± 4	25.3 ± NR	Experienced	Back squat
	Randomized cross-over	10 (10/0)	27 ± 4	25.3 ± NR	Experienced	Back squat
Pérez-López et al.[33]	Pre–Post	14 (14/0)	24.9 ± 4.8	25.6 ± 3.1	Experienced	Leg press, Leg extension
Phillips et al.[92]	Randomized cross-over with control	14 (14/0)	21.7 ± 1.7	25.1 ± 4.1	Experienced	Chest press, seated row, leg extension, leg curl, shoulder press, lat pull down, leg press, chest fly
	Randomized cross-over with control	14 (14/0)	21.7 ± 1.7	25.1 ± 4.1	Experienced	Chest press, seated row, leg extension, leg curl, shoulder press, lat pull down, leg press, chest fly
Pledge et al.[93]	Randomized cross-over with control	12 (12/0)	20 ± 1.6	24.5 ± NR	Inexperienced	Chest press, seated leg press, shoulder press, front latissimus dorsi pull down
	Randomized cross-over with control	12 (12/0)	20 ± 1.6	24.5 ± NR	Inexperienced	Chest press, seated leg press, shoulder press, front latissimus dorsi pull down
Quiles et al.[94]	Pre–Post	8 (8/0)	23 ± 3	NR	Experienced	Squat, bench press
	Pre–Post	7 (7/0)	23 ± 3	NR	Experienced	Squat, bench press
Rossi et al.[95]	Randomized cross-over	8 (8/0)	24.6 ± 4.1	24 ± NR	Experienced	Squat, bench press
	Randomized cross-over	8 (8/0)	24.6 ± 4.1	24 ± NR	Experienced	Squat, bench press

Volume sets × reps; rest (min); Con: Ecc (s)	Intensity	Dose (volume × intensity)	Time of day	Analysis method	Myokines	Hedges' g
(6 × 2) × 10 plus 1 set until movement failure; 1.5	65% of 1 RM	10 530	6:30–9:30	ELISA	IL-6, IL-10	↓, ↑↑
(3 × 5) × 10 plus 1 set until movement failure; 1.5	65% of 1 RM	9230	6:30–9:30	ELISA	IL-6, IL-10	↓↓↓, ↓↓↓
(3 × 5) × 10 plus 1 set until movement failure; 1.5	65% of 1 RM	7800	6:30–9:30	ELISA	IL-6, IL-10	↓, ↑
4 × 10; 2	70% of 1 RM	2800	13:00	Milliplex Human High Sensitivity T Cell Panel	IL-6, IL-10, IL-15	↑, ↑, ↑
4 × 10; 1.5, 0.5 in middle of sets	70% of 1 RM	2800	13:00	Milliplex Human High Sensitivity T-Cell Panel	IL-6, IL-10, IL-15	=, =, ↑
(3 × 4) × 10–12; 1.5; 5:1	60% of 1 RM	7920	6:00–7:00	CBA	IL-6, IL-10, TNF-α	↑, ↑, =
(3 × 4) × 10–12; 1.; 1:5	60% of 1 RM	7920	6:00–7:00	CBA	IL-6, IL-10, TNF-α	↑, =, ↓↓↓
(3 × 4) × until exhaustion; 1	70% of 1 RM	10 990	Morning	CBA	IL-6	↑
4 × 10; 2	70% of 1 RM	2800	NR	ELISA	IL-1ra, IL-6, IL-10	↑, ↑, ↓
4 × 10; 2	70% of 1 RM	2800	NR	ELISA	IL-1ra, IL-6, IL-10	↑↑, ↓, =
2 × 5, then 4 × 10; 3	40–60% of 1RM, then 70% of 1RM	3300	NR	MBMK	IL-6, IL-15	↑↑↑, ↑↑↑
2 × 5, then 4 × 10; 0.5 intraset, 2,5 interset	40–60% of 1RM, then 70% of 1RM	3300	NR	MBMK	IL-6, IL-15	↑↑, ↑↑↑
(2 × 4) × 8–15	75% of 1RM	6900	Morning	ELISA	IL-15	↑↑↑
(8 × 3) × 12 (last set until exhaustion); 2	65% of 1 RM	18 720	NR	ELISA	IL-6	↑↑↑
(8 × 3) × 8 (last set until exhaustion); 2	85% of 1 RM	16 320	NR	ELISA	IL-6	↑↑↑
(4 × 3) × 8–12; 1	70% of 1 RM	6720	08:15–09:00	ELISA	IL-6	↑↑
(4 × 3) × 8–12; 1	70% of 1 RM	6720	18:15–19:00	ELISA	IL-6	=
(2 × 4) × 12, NR	60% of 1RM	5760	NR	ELISA	IL-6	↑↑↑
(2 × 8) × 6, NR	75% of 1RM	7200	NR	ELISA	IL-6	↑
(2 × 4) × until exhaustion; 0.5	70% of 1 RM	4900	NR	ELISA	IL-6, IL-10, TNF-α	↓, NR, NR
(2 × 4) × until exhaustion; 1.5	70% of 1 RM	6650	NR	ELISA	IL-6, IL-10, TNF-α	↑, NR, NR

(Continues)

TABLE 2 (Continued)

Reference	Design	N (m/f)	Age (years), $M \pm SD$	BMI (kg/m²), $M \pm SD$	Resistance training status	Exercises
Şahin et al.[98]	Randomized cross-over	10 (10/0)	21.1 ± 1.2	22.3 ± 3.1	Inexperienced	Squat, deadlift
	Randomized cross-over	10 (10/0)	21.1 ± 1.2	22.3 ± 3.1	Inexperienced	Squat, deadlift
Townsend et al.[101]	Pre–Post	30 (30/0)	22.5 ± 2.7	27.4 ± NR	Experienced	Squat, deadlift, barbell split squat
Vincent et al.[96]	Randomized cross-over	20 (14/6)	26.8 ± 5.9	25.4 ± 4.0	Experienced	Leg extension, leg curl, chest press, seated row, shoulder press, pull down
	Randomized cross-over	20 (14/6)	26.8 ± 5.9	25.4 ± 4.0	Experienced	Leg extension, leg curl, chest press, seated row, shoulder press, pull down
Wells et al.[102]	Randomized cross-over	10 (10/0)	24.7 ± 3.4	29.1 ± NR	Experienced	Barbell back squats, bilateral leg press, bilateral hamstring curls, bilateral leg extension, seated calf raises
	Randomized cross-over	10 (10/0)	24.7 ± 3.4	29.1 ± NR	Experienced	Barbell back squats, bilateral leg press, bilateral hamstring curls, bilateral leg extension, seated calf raises

Abbreviations: = no effect; ↑ small positive effect; ↑↑ moderate positive effect; ↑↑↑ large positive effect; ↓ small negative effect; ↓↓ moderate negative effect; ↓↓↓ large negative effect; BMI, body mass index; CBA, cytometric bead array; CG, control group; con, concentric; ecc, eccentric; ECLIA, electrochemiluminescence; ELISA, enzyme-linked immunosorbent assay; f, female; IG, intervention group; IL, interleukin; kg, kilogram; m², square meter; m, male; M, mean; MBMK, premixed magnetic bead-based multiplex kit; min, minutes; N, numbers; NR, not reported; resp, respectively; Rep, Repetition; RIA, radioimmunoassay; RM, repetition maximum; SD, standard deviation; sec, seconds; TNF-α, tumor-necrosis factor alpha.

confirmed by Egger's test (intercept = −0.87, p = .070), but no adjustments were necessary according to the trim-and-fill analysis (SE = 2.81).

One can note that during the sensitivity analysis, the second intervention group of Lira et al.[55] (g = −1.0) became an influential outlier when using a correlation coefficient of .85 (see section 2.6).

3.5.2 | Moderator analysis (categorical)

Sex
The sex distribution was skewed, with most studies analyzing male participants. Male (k = 19, g = 0.19, 95% CI −0.10; 0.47) and female (k = 5, g = −0.02, 95% CI −0.22; 0.19) groups of participants did not significantly differ (Q_M = 1.74, df = 1, p = .188).

Training status
Samples experienced (k = 15, g = 0.07, 95% CI −0.16; 0.30) and inexperienced with resistance training (k = 9, g = 0.28, 95% CI −0.26; 0.82) did not significantly differ (Q_M = 0.66, df = 1, p = .418).

Type of exercise
As upper body exercise only had one effect (g = 0.37, 95% CI −0.05; 0.79), it was removed from the statistical analysis. The results were not significantly different (Q_M = 1.20, df = 1, p = .273) for full-body (k = 13, g = 0.24, 95% CI −0.14; 0.61) and lower body exercises (k = 10, g = 0.00, 95% CI −0.30; 0.30).

Time of the day
The testing moment was not reported for 68.3% of the effects; thus, this analysis may not represent the full set of studies included in this manuscript. Testing times in the morning (k = 5, g = 0.09, 95% CI −0.71; 0.89) and in the afternoon (k = 5, g = −0.04, 95% CI −0.30; 0.23) did not differ significantly (Q_M = 0.17, df = 1, p = .681).

Risk of bias
The four categories of the risk of bias assessment, low (k = 2, g = 0.12, 95% CI −0.70; 0.93), moderate (k = 8, g = −0.06, 95% CI −0.47; 0.36), serious (k = 8, g = 0.00, 95% CI −0.26; 0.27), and critical (k = 6, g = 0.64, 95% CI −0.05; 1.33) risk of bias were not significantly different (Q_M = 5.56, df = 3, p = .135).

Volume sets × reps; rest (min); Con: Ecc (s)	Intensity	Dose (volume × intensity)	Time of day	Analysis method	Myokines	Hedges' g
(2 × 3) × 8–12; 1.5–2	80% of 1RM	4800	9:00–11:00	ELISA	IL-6, TNF-α	↑↑, ↑↑
(2 × 3) × 8–12; 1.5–2	80% of 1RM	4800	9:00–11:00	ELISA	IL-6, TNF-α	↑, ↑
(3 × 4) × 10; 1.5	70–80% of 1RM	8760	NR	Millipore Milliplex	TNF-α	↑↑
(6 × 2) × 12	60% of 1RM	8640	8:30–13:00	Milliplex MAP kit	IL-6, TNF-α	=, =
(6 × 2) × 10	100% of 1RM ECC, 50% of 1 RM CON	9000	8:30–13:00	Milliplex MAP kit	IL-6, TNF-α	↑, ↑
(1 × 6 + 4 × 4) × 10–12; 1	70% of 1RM	16 940	Morning	Multiplex cytokine assay	TNF-α	↑↑↑
(1 × 6 + 4 × 4) × 3–5; 3	90% of 1RM	7920	Morning	Multiplex cytokine assay	TNF-α	↑↑

3.5.3 | Moderator analysis (continuous)

Age
Meta-regression revealed that the age of participants was not a significant moderator of the immediate IL-10 response to exercise ($k = 24$, $R^2 = 0\%$, $p = .719$). It must be considered that the meta-regression was based on mean age values and did not necessarily represent the sample homogeneously.

Exercise volume
Meta-regression revealed that the exercise volume was not a significant moderator of the immediate IL-10 response to exercise ($k = 24$, $R^2 = 0\%$, $p = .855$).

Exercise intensity
Meta-regression revealed that the exercise intensity was not a significant moderator of the immediate IL-10 response to exercise ($k = 24$, $R^2 = 0\%$, $p = .503$).

Exercise dose
Meta-regression revealed that the exercise dose was not a significant moderator of the immediate IL-10 response to exercise ($k = 24$, $R^2 = 0\%$, $p = .742$).

3.5.4 | Moderator analysis (multivariate)

Time of the day was not considered in the multivariate analysis to avoid losing all studies not reporting this information. The model considered in the multivariate analysis (including sex, age, training status, exercise dose, exercise type, training status × exercise dose, and exercise type × exercise dose) was not significant (coeff. 2:9; $F(8, 15) = 0.426$, $p = .897$, $R^2 = 0\%$).

3.6 | Interleukin-1ra

3.6.1 | Main analysis

The average effect size for IL-1ra was large ($k = 14$, $g = 0.71$, $p < .001$), and its confidence interval was between 0.48 and 0.94, which indicates that in a universe of comparable studies to the one included in this analysis, the mean effect size could fall anywhere in between moderate and large (Figure S3). This range did not include 0, which revealed that the true effect is very likely to be positive and equal or beyond moderate. The heterogeneity was moderate to large (PI [0.01; 1.41], $\tau^2 = 0.09$),

TABLE 3 Risk of bias assessment.

References	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to missing data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall result
Agostinete et al.[77]	−−	++	++	++	++	++	Critical risk
Barquilha et al.[100]	−−	−	−−	+	++	+	Critical risk
Benini et al.[74]	++	++	−	++	++	++	Serious risk
Brenner et al.[78]	−	++	++	++	++	++	Serious risk
Bugera et al.[105]	+	++	++	+	++	−	Serious risk
Cui et al.[79]	++	+	++	++	++	+	Moderate risk
Fatouros et al.[80]	−	++	++	++	++	++	Serious risk
Gadruni et al.[81]	−−	+	−	++	++	++	Critical risk
Gerosa-Neto et al.[75]	−	++	+	++	++	+	Serious risk
Gordon et al.[76]	−	++	+	++	++	+	Serious risk
Goto et al.[82]	+	+	++	++	++	++	Moderate risk
Heavens et al.[99]	++	++	+	++	++	++	Moderate risk
He et al.[104]	+	++	++	++	++	−	Serious risk
Ihalainen et al.[84]	−−	++	++	++	++	++	Critical risk
Ihalainen et al.[83]	−−	++	++	++	++	++	Critical risk
Izquierdo et al.[85]	−−	+	+	++	++	++	Critical risk
Joisten et al.[86]	++	+	++	++	++	++	Moderate risk
Krüger et al.[87]	+	++	++	++	++	++	Moderate risk
Lira et al.[55]	++	++	++	++	++	+	Moderate risk
Lipford et al.[103]	++	++	++	++	++	+	Moderate risk
Luk et al.[88]	++	++	++	++	++	++	Low risk
Marucci-Barbosa et al.[89]	−	+	+	++	++	+	Serious risk
Nakajima et al.[90]	−−	+	+	++	++	++	Critical risk
Notbohm et al.[97]	+	++	++	++	++	++	Moderate risk
Oliver et al.[91]	−	+	++	++	++	++	Serious risk
Pérez-López et al.[33]	−−	+	++	+	++	++	Critical risk
Phillips et al.[92]	+	++	++	++	++	+	Moderate risk
Pledge et al.[93]	+	++	++	++	++	++	Moderate risk
Quiles et al.[94]	++	+	++	++	++	++	Moderate risk
Rossi et al.[95]	−	++	+	++	++	++	Serious risk
Şahin et al.[98]	−	−	++	+	++	−	Serious risk
Townsend et al.[101]	−−	+	++	+	++	+	Critical risk
Vincent et al.[96]	−−	−	++	++	++	++	Critical risk
Wells et al.[102]	+	+	++	++	++	+	Moderate risk

Note: ++ Low risk, + Moderate risk, − Serious risk, −− Critical risk.

TABLE 4 Results meta-analyses.

	IL-6	IL-10	IL-1ra#	TNF-α	IL-15
g [95% CI]	0.45 [0.29; 0.61]**	0.14 [−0.09; 0.39]	0.49 [0.24; 0.75]***	0.31 [0.07; 0.55]*	0.35 [0.01; 0.69]*
PI	[−0.74; 1.65]	[−0.93; 1.20]	[−0.52; 1.51]	[−0.55; 1.17]	[−0.49; 1.19]
I^2	75.6%	73.8%	77.6%	69.8%	63.2%
k	56	24	19	15	7
Participants	404 (174[a])	178 (73[a])	61 (40[a])	123 (83[a])	64 (33[a])
Tested moderators	Sex, training status, type of exercise, time of day, risk of bias, age, exercise volume, exercise intensity, exercise dose	Sex, training status, type of exercise, time of day, risk of bias, age, exercise volume, exercise intensity, exercise dose	Training status, age, exercise volume, exercise intensity, exercise dose	Training status, type of exercise, risk of bias, exercise volume, exercise intensity, exercise dose	Exercise volume, exercise intensity, exercise dose

Abbreviations: CI, confidence interval; g, Hedges' g; IL, interleukin; k, number of studies included; PI, prediction interval.

[a]Participants counting for at least two effect sizes.

#Values adjusted based on trim-and-fill analysis.

*$p < .05$; **$p < .01$; ***$p < .001$.

with a moderate part representing the variance of the true effect ($I^2 = 54.5\%$). According to the PI, in the universe of populations represented by the included studies, the true effect in 95% of cases will fall between small and large positive effects. No influential outliers were detected. Visual asymmetry was assumed and confirmed by Egger's test (intercept $= -1.43$, $p < .001$). The trim-and-fill analysis showed five missing effects on the left side ($SE = 2.43$, Figure 2B). With these five missing effects imputed, the average effect size was reduced to moderate but remained significant ($p < .001$), $k = 19$, $g = 0.49$ (95% CI: 0.24; 0.75).

One can note that while the asymmetry was always evident in the sensitivity analysis, no missing studies were required when using correlation coefficients of .75, .80, .85 (see section 2.6).

3.6.2 | Moderator analysis (categorical)

Only one study reported using females, one study reported doing full-body exercises, while all others did lower body exercise,[77] all studies were ranked with a critical risk of bias, and no study reported the testing time; thus, no moderator analyses were performed for sex, exercise type, risk of bias, and testing time.

Training status
Samples experienced ($k = 8$, $g = 0.70$, 95% CI 0.36; 1.04) and inexperienced with resistance training ($k = 6$, $g = 0.73$, 95% CI 0.28; 1.17) did not significantly differ ($Q_M = 0.01$, $df = 1$, $p = .912$).

3.6.3 | Moderator analysis (continuous)

Age
Meta-regression revealed that the age of participants was not a significant moderator of the immediate IL-1ra response to exercise ($k = 14$, $R^2 = 0\%$, $p = .308$). It must be considered that the meta-regression was based on mean age values and did not necessarily represent the sample homogeneously.

Exercise volume
Meta-regression revealed that the exercise volume was not a significant moderator of the immediate IL-1ra response to exercise ($k = 14$, $R^2 = 0\%$, $p = .717$).

Exercise intensity
Meta-regression revealed that the exercise intensity was not a significant moderator of the immediate IL-1ra response to exercise ($k = 14$, $R^2 = 0\%$, $p = .532$).
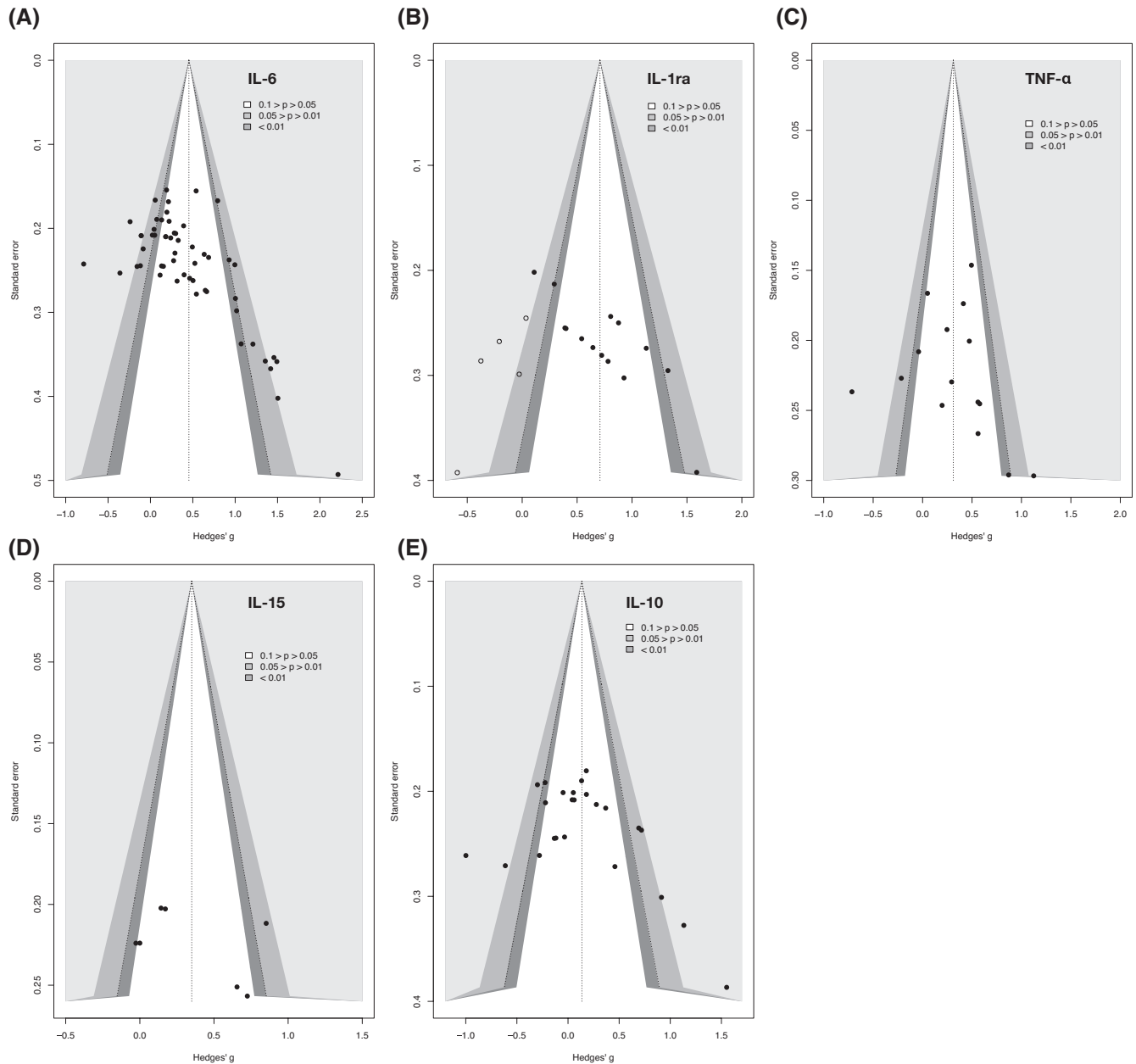
(A) **(B)** **(C)**

(D) **(E)**

FIGURE 2 Funnel plot for IL-6 (A), IL-1ra (B), TNF-α (C), IL-15 (D), and IL-10 (E). Black circles indicate actual effects, white circles indicate missing effect.

Exercise dose

Meta-regression revealed that the exercise dose was not a significant moderator of the immediate IL-1ra response to exercise ($k = 14$, $R^2 = 0\%$, $p = .822$).

3.6.4 | Moderator analysis (multivariate)

The model considered in the multivariate analysis (including age, training status, exercise dose, and training status × exercise dose) was not significant (coeff. 2:5; $F(4, 9) = 1.404$, $p = .471$, $R^2 = 0\%$).

3.7 | TNF-α

3.7.1 | Main analysis

The average effect size for TNF-α was small to moderate ($k = 15$, $g = 0.31$, $p < .050$), and its confidence interval was between 0.07 and 0.55, which indicates that in a universe of comparable studies to the one included in this analysis, the mean effect size could fall anywhere in between very small and moderate (Figure S4). According to its studentized residuals and DFBETA, the second intervention group of Marucci-Barbosa et al.[89] was considered

an influential outlier, resulting in a re-analysis conducted without its inclusion. The average effect slightly increased ($k = 14$, $g = 0.37$, $p < .010$), and its confidence interval was between 0.18 and 0.56. This range did not include 0, revealing that the true effect is likely to be positive and equal or beyond small. The heterogeneity was large (PI [−0.25; 0.99], $\tau^2 = 0.07$), with a moderate part representing the variance of the true effect ($I^2 = 52.4\%$). According to the PI, in the universe of populations represented by the included studies, the true effect in 95% of cases will fall between small negative and large positive effects. No asymmetry was detected (intercept = −.13, $p = .224$) (Figure 2C).

One can note that during the sensitivity analysis, the second intervention group of Marucci-Barbosa et al.[89] ($g = -0.71$) was not an influential outlier when using correlation coefficients of .55, .60, .65 (see section 2.6).

3.7.2 | Moderator analysis (categorical)

Only one study reported using participants of both sexes, and none reported using females only, and studies reporting the testing time were all performed in the morning; thus, no moderator analyses (univariate and multivariate) were performed for sex and testing time.

Training status
Samples experienced ($k = 8$, $g = 0.46$, 95% CI 0.15; 0.77) and inexperienced with resistance training ($k = 6$, $g = 0.26$, 95% CI −0.02; 0.54) did not significantly differ ($Q_M = 1.41$, $df = 1$, $p = .236$).

Type of exercise
The results were not significantly different ($Q_M = 0.02$, $df = 1$, $p = .991$) for full-body ($k = 5$, $g = 0.37$, 95% CI −0.01; 0.75), upper body ($k = 7$, $g = 0.38$, 95% CI −0.02; 0.78), and lower body exercises ($k = 2$, $g = 0.36$, 95% CI −1.08; 1.79).

Risk of bias
The three categories of the risk of bias assessment, moderate ($k = 3$, $g = 0.18$, 95% CI −0.68; 1.04), serious ($k = 8$, $g = 0.48$, 95% CI 0.18; 0.79), and critical ($k = 3$, $g = 0.32$, 95% CI −0.26; 0.91) risk of bias were not significantly different ($Q_M = 1.80$, $df = 2$, $p = .408$).

3.7.3 | Moderator analysis (continuous)

The moderator age was disregarded as having a very small range (21–27 years) in a relatively small sample of studies.

Exercise volume
Meta-regression revealed that the exercise volume was not a significant moderator of the immediate TNF-α response to exercise ($k = 14$, $R^2 = 0\%$, $p = .690$).

Exercise intensity
Meta-regression revealed that the exercise intensity was not a significant moderator of the immediate TNF-α response to exercise ($k = 14$, $R^2 = 1.8\%$, $p = .280$).

Exercise dose
Meta-regression revealed that the exercise dose was not a significant moderator of the immediate TNF-α response to exercise ($k = 14$, $R^2 = 1.5\%$, $p = .337$).

3.7.4 | Moderator analysis (multivariate)

The model considered in the multivariate analysis (including training status, exercise dose, exercise type, training status × exercise dose, and exercise type × exercise dose) was not significant (coeff. 2:8; $F(7, 7) = 1.304$, $p = .368$, $R^2 = 25.0\%$).

3.8 | Interleukin-15

3.8.1 | Main analysis

The average effect size for IL-15 was moderate ($k = 8$, $g = 0.52$, $p < .050$), and its confidence interval was between 0.02 and 1.02, which indicates that in a universe of comparable studies to the one included in this analysis, the mean effect size could fall anywhere in between null and large (Figure S5). According to its studentized residuals and DFBETA, Pérez-Lopez et al.[33] were recognized as an influential outlier, resulting in a re-analysis conducted without its inclusion. The average effect decreased, but remained significant ($k = 7$, $g = 0.35$, $p < .050$), and its confidence interval was between 0.01 and 0.69. This range did not include 0, which revealed that the true effect is very likely to be positive. The heterogeneity was large (PI [−0.49; 1.19], $\tau^2 = 0.09$), with a moderate to large part representing the variance of the true effect ($I^2 = 63.2\%$). According to the PI, in the universe of populations represented by the included studies, the true effect in 95% of cases will fall between moderate negative and large positive effects. There were not enough studies to test for asymmetry, yet no evident visual asymmetry was detected (Figure 2D).

One can note that during the sensitivity analysis, Pérez-Lopez et al.[33] ($g = -0.71$) was not an influential

outlier when using correlation coefficients of .55 and .60 (see section 2.6).

3.8.2 | Moderator analysis (continuous)

Only one study reported using females only, one study had a different rating of bias than the others (low vs. serious), only two studies reported the testing time, and all included studies reported testing experienced participants on lower body exercise; thus, no categorical moderator analysis was performed. The moderator age was also disregarded as having a very small range (23–27 years) in a small sample of studies.

Exercise volume

Meta-regression revealed that the exercise volume was not a significant moderator of the immediate IL-15 response to exercise ($k=7$, $R^2=35.3\%$, $p=.135$).

Exercise intensity

Meta-regression revealed that the exercise intensity was not a significant moderator of the immediate IL-15 response to exercise ($k=7$, $R^2=0\%$, $p=.583$).

Exercise dose

Meta-regression revealed that the exercise dose was not a significant moderator of the immediate IL-15 response to exercise ($k=7$, $R^2=47.6\%$, $p=.096$). One can note that during the sensitivity analysis, exercise dose reached significance when a correlation coefficient of .55 was used (see section 2.6).

4 | DISCUSSION

This systematic review and meta-analysis aimed to examine the effects of acute resistance exercise on the release of the immunoregulatory myokines IL-6, IL-10, IL-1ra, TNF-α, IL-15, IL-7, TGF-β1, and FKN. A second aim was to characterize how different exercise parameters may influence this response. To the authors' knowledge, this article is the first to statistically evaluate the change in concentration of IL-6, IL-10, IL-1ra, TNF-α, and IL-15 from baseline to immediately post-exercise in relation to different moderators.

4.1 | Main results

Thirty-four studies were included in this systematic review, of which 29 were considered for the meta-analysis investigating IL-6 ($k=56$), 11 for IL-10 ($k=24$), 5 for IL-1ra ($k=14$), 9 for TNF-α ($k=15$), and 5 for IL-15 ($k=8$).

The main findings were a moderate positive effect of resistance exercise for IL-6 and IL-1ra. Regarding IL-15 and TNF-α, small to moderate effects were found. No significant results were detected for IL-10. For all five meta-analyses, the overall heterogeneity was moderate to large, with only a moderate to large part of this heterogeneity representing the variance of the true effect. Asymmetry suggesting eventual small-study effects or publication bias was detected for all five meta-analyses. Due to no data, no meta-analyses could be performed for IL-7, TGF-β1, and FKN.

4.1.1 | IL-6

Forty-eight intervention groups investigating IL-6 documented a positive effect immediately post-exercise, resulting in a significantly moderate positive average effect. This post-exercise increase in circulating IL-6 levels has also been a consistent finding among studies employing endurance exercise protocols.[18,21,106,107]

The mobilization of leukocytes into the bloodstream during exercise, coupled with the heightened transcriptional activity of inflammatory genes in peripheral blood mononuclear cells, indicates that immune cells play a role in the post-exercise elevation of IL-6.[108,109] IL-6 can stimulate the differentiation of B cells into antibody-producing plasma cells and the growth and differentiation of T cells,[110] especially CD4+ T cells, by determining their effector functions.[111] As IL-6 contributes to the differentiation of T helper cells and the production of further cytokines such as IL-4, IL-21, and IL-17,[111] cellular and humoral immunity can be enhanced. In the regenerating muscle, IL-6 is released by infiltrating neutrophils and macrophages,[112] by fibro-adipogenic progenitors,[113] and by satellite cells,[114,115] suggesting possible autocrine and paracrine functions of IL-6 in satellite cell-dependent myogenesis.[116] However, accumulating evidence from biopsy, gene sequencing, or blood sampling studies[24,117,118] indicates that IL-6 release from the myocytes of the working muscle is far more important than that of immune cells.

Making a distinction between the originating tissue and the environmental context is of significant importance, as it determines the effect of IL-6. Specifically, the release of IL-6 by immune cells is usually accompanied by IL-1β and TNF-α co-secretion and thus triggers pro-inflammatory signaling cascades and neutrophil infiltration that ultimately mediate tissue repair.[14] In contrast, the release of IL-6 by the skeletal muscle is not triggered by immune cell signaling but by augmented calcium signaling, glycogen depletion, and lactic acid accumulation.[119] The fact that muscle-derived IL-6 is released in response

to energetic stress indicates its main tasks: liberating energy, enhancing muscular energy uptake, and transiently dampening immune system activity.[119] To achieve the latter, muscle-derived IL-6 inhibits the production of TNF-α, while promoting the synthesis of IL-10 and IL-1ra, without activating classical pro-inflammatory pathways.[5] However, the results of this meta-analysis show that TNF-α is significantly increased following an acute session of resistance exercise, while there was no significant result regarding IL-10. Consequently, it appears that it is not the increase in muscle-derived IL-6 but other factors that are responsible for the TNF-α and IL-10 response to (resistance) exercise.

In addition, as the skeletal muscle also consumes carbohydrates during exercise, several myokines, among others IL-6, promote the expression of glucose transporter 4 in skeletal muscles and increase muscular insulin sensitivity, thus lowering plasma glucose concentrations during exercise and up to 24 h afterward.[14,119] Furthermore, IL-6 increases lipolysis in skeletal muscle[1,120] as well as fat oxidation in adipose tissue via activation of 5′ adenosine monophosphate-activated protein kinase (AMPK),[121-123] reducing adipose tissue with inflammatory capacity. Additionally, it mediates crosstalk between insulin-sensitive tissues, the gut, and pancreatic islets to adapt to changes in insulin demand by increasing glucagon-like peptide-1 secretion.[116]

4.1.2 | IL-10

Unexpectedly, based on the studies included in the meta-analysis, we could not find a significantly positive average effect for IL-10 immediately post-exercise, indicating that the IL-10 increments elicited by an acute resistance exercise bout might either be less pronounced or delayed compared to the other investigated myokines.

Given the previously mentioned IL-6-stimulated release of IL-10 during exercise, this finding might come as a surprise but may be rooted in the kinetic of its activation. Specifically, it has been demonstrated that in contrast to IL-6, monocytes and lymphocytes are the primary sources of circulating IL-10 in response to exercise.[124,125] As endurance exercise generally causes greater activation of leukocytes due to cardiovascular demands,[126] an increase in IL-10 is more likely after endurance exercise. Consequently, it is conceivable that the employed resistance exercise schemes were not able to induce sufficiently high levels of IL-6 to stimulate significant IL-10 release, potentially due to a short duration and their intermittent character. Drawing a comparison with studies on endurance exercises, it has been observed that prolonged cycling for a minimum of 1 h

led to notable elevations in IL-10, as reported by Nieman et al.[127] and Ulven et al.[18] However, investigations utilizing shorter durations revealed only minor increases in IL-6 and did not show significant changes in IL-10, as demonstrated by Cullen et al.[124] and Markovitch et al.[125] Hence, the authors concluded that the induced IL-6 increase might not have been sufficient to induce downstream systemic anti-inflammatory responses immediately post-exercise.[124]

Beyond that, it may be important to consider that the kinetic of IL-10 activation through IL-6 has a second branch passing by the kynurenine pathway, potentially requiring more delay and thus not detected in our analysis. Indeed, the exercise-induced IL-6 increase activates the indoleamine 2,3-dioxygenase and kynurenine 3-monooxygenase enzymes, producing more kynurenine and kynurenic acid.[20,128] These metabolites are ligands to the transcription factor aryl hydrocarbon receptor, promoting the differentiation of naïve CD4+ T cells to regulatory CD4+ T cells that are the main producers of anti-inflammatory cytokines, including IL-10.[20] As muscle contraction-induced IL-6 peaks at the end of the exercise, many studies included in this review also reported a continued IL-10 release between 30 and 60 min post-exercise.[55,74,75,77]

In addition to physiological considerations, it has also to be considered that methodological features of the included studies might have influenced the results of the meta-analysis. Yet, looking at the two studies with the largest negative effect, no obvious explanation becomes apparent. While Lira et al.[55] ($g = -1.00$) was assessed to be at moderate risk of bias and did not show any remarkable characteristics for the participants nor the intervention itself, Brenner et al.[78] neither controlled for the physical activity before exercise nor reported an identical warm-up for all participants which might serve as the best explanation for the divergent results. Still, it is not entirely clear what factors can explain the variability in IL-10 results, highlighting the need for further research.

Immunologically, increased levels of IL-10 contribute to an anti-inflammatory environment by inhibiting the synthesis of proinflammatory cytokines as well as MHC class II and co-stimulatory molecules in activated macrophages/monocytes.[19] Moreover, IL-10 blocks the release of IL-1α, IL-1β, and TNF-α as well as the production of chemokines, including IL-8 and macrophage inflammatory protein-α from lipopolysaccharide-activated human monocytes.[129,130] Additionally, it not only inhibits the synthesis of these effectors but also increases the expression of their natural antagonists.[131] IL-10 is also the principal cytokine that suppresses cell-mediated immunity and dendritic cell maturation.[131] For the working muscle, these anti-inflammatory effects of IL-10 and IL-1ra are of significant importance to ensure energy supply by

limiting the energy expenditure of the immune system.[119] Additionally, IL-10 has been reported to prevent insulin resistance in the muscle.[132]

4.1.3 | IL-1ra

The results of the meta-analysis revealed a moderate positive average effect for IL-1ra, supporting our hypothesis that resistance exercise bouts result in acute increases of IL-1ra. Our results align with previous studies employing other exercise forms showing that running[133] and cycling[109] lead to significant increases in IL-1ra levels and gene expression immediately postexercise and within 1-h postexercise, respectively. During and after exercise, IL-1ra is predominantly released by macrophages upon IL-6 stimulation.[14,134] The increased circulating levels become functionally relevant as IL-1ra exerts anti-inflammatory effects by inhibiting IL-1β signal transduction, without inducing any intracellular response.[14,135]

4.1.4 | TNF-α

This meta-analysis showed a small positive average effect for TNF-α caused by an acute session of resistance exercise. However, there were also two studies showing negative effect sizes.[89,103] In the study by Marucci-Barbosa et al.[89] in particular, the results were unexpected, as the intervention group focusing on the eccentric phase (1 s concentric, 5 s eccentric) demonstrated the most prominent decrease in TNF-α levels ($g = -.71$). Since eccentric training leads to greater muscle damage and thus to a stronger immune response,[136] it could have been assumed that this intervention group, in particular, would show a significant increase in TNF-α concentrations after resistance training, giving rise to the assumption that muscle fiber damage might not be the primary trigger of acute TNF-α release.

Nevertheless, a decrease could have been expected as muscle-derived IL-6 is presumably not activating pro-inflammatory pathways, which would include an increase in TNF-α, but it is postulated that it is leading to an anti-inflammatory environment.[1,14] However, this increase in TNF-α post-exercise seems to be stable over time as literature shows elevated levels also 15, 30, 60, and 120 min after exercise cessation.[75,102] It, therefore, seems that it is not the increase in muscle-derived IL-6, but other factors leading the reaction of TNF-α in response to (resistance) exercise. An increase in macrophages, the main source of TNF-α,[137] released due to the exercise-induced immunological stress response,[138] may be one of the main causes for the increase in TNF-α after

exercise. This is also true for other forms of exercise, like moderate to vigorous endurance exercise.[18,139-141] In addition, studies examining TNF-α in biopsy samples in response to resistance training found a significant increase in TNF-α mRNA expression immediately after exercise, peaking 8 h after exercise.[73]

4.1.5 | IL-15

The results of the meta-analysis revealed a small positive average effect for IL-15. Based on results in the literature that could not be proven for endurance exercise.[42,47] IL-15 has been previously demonstrated to trigger anabolic effects,[142] which are more likely to be provoked by resistance exercise rather than endurance exercise. Furthermore, it stimulates protein accumulation and the accretion of myosin heavy chains in differentiated myotubes and myocytes and simultaneously reduces protein degradation.[143-145] As it is also involved in reducing white adipose tissue[142] and increasing glucose tolerance,[146] IL-15 reduces systemic inflammation.

The examination of biopsy samples shows that the mRNA expression of IL-15 in skeletal muscles is increased immediately after exercise and reaches a significant level 4 h post-exercise.[33] This could explain the only small positive effect found by this meta-analysis and suggests that further investigations are necessary at other time points post-exercise.

4.1.6 | IL-7, TGF-β1, and FKN

No study investigated the effects of resistance exercise on IL-7 immediately post-exercise in healthy individuals. Looking at other forms of exercise not included in this analysis, one study investigated the acute changes in IL-7 in response to endurance exercise.[22] They demonstrated a significant increase 3 h postexercise but no significant change immediately after exercise cessation. Furthermore, only the trained but not the untrained intervention group reached significance. Overall, further research on IL-7 in response to any form of exercise is needed to clarify whether exercise has a significant effect on IL-7 levels.

Additionally, no study investigated changes in TGF-β1 concentration in response to resistance exercise. One study conducted by Heinemeier et al.[147] investigated changes in the expression of TGF-β1 following kicking exercises, showing a significant increase in TGF-β1 expression levels as well as their receptors. It can, therefore, be assumed that TGF-β1 is produced upon exercise. As TGF-β is an important factor driving regulatory CD4+ T-cell generation, one can speculate that exercise produced TGF-β1 could control

for potential muscle inflammation in sterile conditions. However, more targeted research into specific forms of exercise is required to develop more specific training measures for different disease groups and their therapy.

Regarding FKN, there is no study investigating their changes immediately post-exercise. However, a study by Della Gatta et al.[148] looks into FKN changes 2 to 24h after resistance exercise cessation. They were taking muscle biopsies from the vastus lateralis after three sets of leg press, squat, and leg extension at 80% 1RM. Two hours after the intervention finished, FKN was significantly elevated, with values doubling from baseline to post-exercise. Although further research is needed to confirm these results, this is already an indication of the potential effect of resistance exercise on FKN. FKN acts on T lymphocytes and monocytes,[149] while soluble FKN regulates the migration of leukocytes.[150]

4.2 | Moderator analysis

We performed moderator analyses for multiple categorical and continuous moderators to test if they were able to explain the heterogeneity of the effect. However, none of the moderator analyses (univariate or multivariate) revealed an effect of exercise volume, intensity, or dose on changes in IL-6, IL-10, IL-1ra, TNF-α, and IL-15 concentration following resistance exercise.

Pedersen et al.[8] showed that the magnitude of the post-endurance exercise increase in plasma IL-6 could be explained by the duration and intensity of exercise and the muscle mass involved in mechanical work. However, our meta-analysis could not confirm this assumption for resistance exercise. This might be because IL-6 production during exercise is strongly linked to the local metabolism and signals of metabolic and hormonal stress.[119] While for endurance exercises, glycogen depletion, lactic acid accumulation, or redox signaling increases with duration and intensity of exercise, for resistance exercise volume might be a more reliable surrogate of metabolic stress, as it is positively correlated with the number of muscle contractions and duration of mechanical work. Specifically, exercising with higher intensities allows fewer repetitions than exercising with lower intensities, thus constituting more of a neuromuscular than a metabolic challenge. For instance, the study conducted by Phillips et al.[92] comparing low-intensity and high-intensity resistance exercises showed that higher exercise doses lead to greater IL-6 changes. In other words, IL-6 levels increased immediately after exercise for both exercises, but the increase was greater in the low-intensity group. Yet, here again, this assumption cannot be confirmed by our results.

The moderator analysis for IL-10 revealed that neither exercise volume, intensity, nor dose significantly moderated its response to an acute bout of resistance exercise. The literature describes the influence of exercise dose on IL-10 and IL-1ra levels equivocally. For example, it has been suggested that changes in IL-1ra and IL-10 post-exercise are determined by the initial changes elicited in the concentration of IL-6.[14] In contrast to that, Ihalainen et al.[84] suggested that changes in IL-1ra concentration depend on the type of resistance exercise and less on IL-6. In a systematic review, Cabral-Santos et al.[151] investigated the response of IL-10 after acute exercise sessions in healthy adults and could not find an evident relationship between intensity and changes in IL-10 production. However, in contrast to our results, they reported a significant linear correlation between exercise duration and deviations of IL-10 from baseline after an acute resistance exercise session. Nevertheless, since this systematic review also included endurance training studies and did not distinguish between endurance and resistance exercise, it must be expected that their results may not be representative of resistance exercise. In addition, it must be taken into account that most of the studies that investigated endurance training sessions were based on long-distance runs, for example, marathons.[152-154] Compared to resistance training studies such as those included in this meta-analysis, there is a large discrepancy between the duration of endurance training and the duration of resistance training, which is usually about 60min of intermittent training.[74,82]

Beyond that, based on the included studies, this meta-analysis showed that the resistance training status could not explain any percentage of the variance between the studies. However, the definition of "resistance exercise experienced" is very broad since participants were considered inexperienced if they were described as untrained or sedentary or did not participate in any kind of regular resistance training 6 months before testing. While the participants in the study by Goto et al.[82] performed resistance training regularly for several years, those investigated by Ihalainen et al.[83] only trained for 3 months before the testing. Thus, great differences even within this definition can occur, and the result regarding this moderator must be treated cautiously.

The moderator age did not help to explain the differences between the study results for Il-6, IL-10, IL-1ra, TNF-α, and IL-15. The mean age range (19–47 years) from the studies included in this analysis was relatively constrained and potentially not perfectly representative of each sample, especially for the analyses of IL-1ra, TNF-α, and IL-15. It would be important, especially for older adults, to find out if their myokine response to resistance exercise is different as optimal muscle aging and optimal

metabolic control, both related to the release of muscle-derived IL-6, are indispensable factors in healthy aging.[155] Therefore, meta-research with elderly participants should be conducted in the future.

Concerning biological sex, only a few studies tested the acute effects of an acute bout of resistance training on IL-6, IL-10, IL-1ra, TNF-α, and IL-15 in women only.[74,88] For example, Benini et al.[74] tested the myokine concentration changes in response to resistance exercise in men and women simultaneously. They found a significant difference between the male and female intervention groups, with men displaying significantly higher concentration changes immediately post-exercise than women, whereas the female intervention group did not show any significant alteration at all. The authors also hypothesized that differences would occur, as there are sex-specific differences in, for instance, muscular fatigue[156] or the inflammatory response following exercise,[157] and different hormonal profiles in general. However, the small number of studies comparing male and female subjects allows no firm conclusions to be drawn about the influence of biological sex on myokine release. Therefore, it is essential to conduct further investigations exploring the differences between men and women and for future studies to avoid mixing results between sexes, as the kinetic of myokine activation might be different.

The testing time point of the intervention (morning or afternoon) was not a significant moderator in any of the meta-analyses. However, as this was only reported in 68.9% of the studies, this moderator may not be well represented in the available data. Pledge et al.[93] were the only ones looking into the difference between a morning and afternoon resistance training session. They were not able to find a significant difference between the exercising groups. However, the control group displayed significantly different baseline values depending on the time point, which may lead to the assumption that IL-6 concentration fluctuates over the day. Therefore, it is indispensable for future studies to report this parameter to enable a better assessment of this moderator.

The outcome of the risk of bias assessment was also not a significant moderator of the results. One might have expected that the poor quality of a study could generally have led to slightly different results. However, this could not be proven with the available data, which indicates that the results are nevertheless stable with varying study quality.

4.3 | Limitations and perspectives

Despite important findings, the results of this systematic review and meta-analysis should be interpreted within the context of its limitations. First, although we are assessing myokines, the data used for our analyses are taken from peripheral blood and not from muscle biopsies. Therefore, we are not measuring muscle-derived cytokines only, but all circulating cytokines including those expressed by other secretory organs as well. Nonetheless, as mentioned previously already, accumulating data from biopsy, gene sequencing, and blood collection studies indicate that the elevation of cytokines originating from active muscle myocytes holds greater significance in promoting systemic increase compared to those released by immune cells.[7,22,23]

Second, while our results assess concentration changes immediately post-exercise, further (meta) research is required to evaluate if an effect dose–response relationship can be displayed when assessing later post-exercise time points (e.g., between 5 min and 3 h post-exercise). However, some studies also collected data at later measurement time points. Comparing the concentration changes of IL-6, IL-10, IL-1ra, TNF-α, and IL-15, there appears to be altered temporal kinetics between endurance and resistance exercise. While it is clearly stated for endurance exercise that peak IL-6 is reached at the end of exercise or shortly thereafter, followed by a rapid decline to baseline levels,[158,159] for resistance exercise, the time course seems to be much more inconsistent. Moreover, since the exercise-induced production of IL-10 is stimulated by IL-6,[160] it could have been assumed that the time course of IL-10 follows the one from IL-6. Unexpectedly, the concentration of IL-10 shows almost a U-shaped curve with great changes directly after exercise and 45 to 60 min post-exercise. Islam et al.[19] pointed out that, especially when taking low- to moderate-intensity exercise into account, small to no differences were observed in IL-6 concentration compared to non-exercising control groups, whereas a significant change in IL-10 could be observed.[161,162] Therefore, due to these inconsistencies in IL-6 but consistent findings for IL-10, it might be questionable whether this relationship between IL-6 and IL-10 is causal[19] or if additional factors have a greater influence on IL-10 concentration. TNF-α is acutely elevated immediately post-exercise and seems to stay on that level for several hours before it returns to baseline, thus remaining unaffected by changes in IL-6 concentration.[75,102] Regarding IL-1ra and IL-15, no firm conclusions can be drawn about changes over time after exercise cessation as no significant data are available. Based on these preliminary results, especially high-quality studies, controlling for confounding variables as well as reporting results properly, on which meta-research can be based are needed to provide further insight into the changes in myokine concentrations after endurance as well as resistance exercise over time.

Third, we used exercise volume and intensity in the current review to compute the resistance exercise dose. Yet, other training parameters might also be highly relevant. For example, inter- and intraset rest or proportion of concentric and eccentric loading could be considered. However, most studies did not capture these parameters to a sufficient extent to use them for quantitative analyses, which increases the need for future studies to investigate the different parameters that influence the dose of resistance training. Fourth, 62% of the studies were deemed to be at either critical or serious risk of bias, and only one study was of very good quality. The most problematic domain was the confounding variables since most were not controlled for or reported. For instance, the time of the day at which testing was executed was not reported in 68.9% of the studies, impairing the possibility of evaluating its effect on the results. Further studies should report this more systematically, as one can assume that it might partially influence the results. This is also true for other confounding variables such as diet or the pre-intervention physical activity, including an identical warm-up for all participants. As the studies aimed to determine the effect of resistance exercise on specific myokines, controlling for physical activity performed before testing is indispensable. Indeed, as physical activity can induce, for example, small inflammatory reactions due to minor muscle damage,[9] it can be assumed that they can also affect the study results if they are not controlled and properly reported. Since the diet also affects the immunological profile and possibly leads to an increase in some inflammatory biomarkers,[163] food intake must be recorded very accurately before testing and should be, at best, standardized for all participants.

Another recurrent problem was the small sample size per study. It not only led to a large variance per study, but also raised questions concerning the representativity of the sample. Finally, some authors also overestimated their effect sizes using the between-subject formula without adjusting it to their within-subject design. This may partly explain why, while the moderator analysis for risk of bias did not show significant differences, the effects in our sample were consistently greater in the five meta-analyses for the studies with a high risk of bias. Overall, to improve the general quality of the studies and their representativeness, it would be necessary to provide more information about confounding variables, such as the time of the day. Moreover, variables such as diet, identical warm-up, or pre-intervention physical activity were not controlled as well as they should have been, and therefore, the risk of bias is increased further. Consequently, future research should focus on precisely describing and controlling these influencing factors, as they may change the results to a large extent. In addition, studies with larger sample sizes are needed to avoid overestimating effect sizes affecting the significance of the results.

5 | CONCLUSION

The results highlighted in this systematic review and meta-analysis showed a moderate positive effect of resistance exercise on IL-6 and IL-1ra. Regarding IL-15 and TNF-α, small to moderate effects were found. This could, however, not be shown for IL-10, potentially due to a large sampling variance and a different kinetic of activation. In general, more data on all myokines is needed concerning training volume and intensity with more consistency in reporting training parameters before and during the training (e.g., reporting the testing time, controlling physical activity and nutritional intake before the testing session, bigger sample sizes, and testing males and females independently), as no clear conclusion on the moderators, in particular, the dose–response relationship can be drawn.

DISCLOSURES
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are openly available on Open Science Framework at https://osf.io/5jkfa/ (doi: 10.17605/OSF.IO/5JKFA).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.