

## PEDIATRIC REVIEW

## Exercise, adipokines and pediatric obesity: a meta-analysis of randomized controlled trials

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**BACKGROUND/OBJECTIVE:** Adipokines are involved in the etiology of diabetes, insulin resistance, and the development of atherosclerosis and other latent-onset complications. The objective of this meta-analysis was to determine the effectiveness of exercise interventions on adipokines in pediatric obesity.

**SUBJECTS/METHODS:** A computerized search was made using three databases. The analysis was restricted to studies that examined the effect of exercise interventions on adipokines (adiponectin, leptin, resistin and visfatin) in pediatric obesity (6–18 years old). Fourteen randomized controlled trials (347 youths) were included. Weighted mean difference (WMD) and 95% confidence intervals were calculated.

**RESULTS:** Exercise was associated with a significant increase in adiponectin (WMD = 0.882  $\mu\text{g ml}^{-1}$ , 95% CI, 0.271–1.493) but did not alter leptin and resistin level. Likewise, exercise intensity and change in body fat; as well as total exercise program duration, duration of the sessions, and change in body fat all significantly influenced the effect of exercise on adiponectin and leptin, respectively.

**CONCLUSIONS:** Exercise seems to increase adiponectin levels in childhood obesity. Our results also suggested that exercise on its own, without the concomitant presence of changes in body composition levels, does not affect leptin levels.

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## INTRODUCTION

Obesity is a growing health concern that has become an epidemic in modern-day society. Adipose tissue is a well-known source of inflammation, and is considered as a complex and highly active metabolic endocrine organ<sup>1</sup> which produces various cytokines.<sup>2</sup> Adipose tissue-derived cytokines or adipokines are involved in the regulation of many processes such as energy metabolism, inflammation, diabetes and atherosclerosis.<sup>3–5</sup> Indeed, increased levels of adipokines and pro-inflammatory cytokines, such as leptin, adiponectin, resistin, apelin or visfatin, tumor necrosis factor- $\alpha$ , and interleukin-6, have prominent roles in the pathogenesis of the metabolic syndrome.<sup>2</sup>

Leptin and adiponectin both are associated with regulation of energy balance and insulin action<sup>6</sup> and obesity negatively affects the levels of these molecules. Leptin also promotes body mass loss decreasing food intake and increasing sympathetic nervous system activity through the hypothalamus.<sup>7</sup> Furthermore, adiponectin has anti-atherogenic, anti-diabetic and anti-inflammatory properties<sup>8</sup> and also play an essential role in maintaining homeostasis in the human body. Another member of the adipocytokine family, resistin was initially perceived as an insulin resistance inducing hormone in mice, but its associations with altered metabolism states were not confirmed in human studies.<sup>9</sup> However, there is growing evidence emphasizing a role of resistin as a pro-inflammatory adipocytokine in humans.<sup>10</sup> In addition, visfatin contribute to vascular disease by inducing endothelial dysfunction through a variety of mechanisms.<sup>11,12</sup>

Regular exercise has been shown to promote positive adaptations and act as adjuvant for obesity prevention and treatment. Regular exercise can potentially modify metabolic hormones and is considered an important treatment of chronic inflammation<sup>13</sup> and obesity-related conditions.<sup>14</sup> The magnitude of benefits may vary with the type and amount of exercise. A systematic review in adults showed that the effect of chronic exercises on leptin and adiponectin concentrations revealed disparate findings.<sup>15</sup> In patients with type 2 diabetes, a recent meta-analysis showed that aerobic exercise program was associated with a significant change in leptin ( $-3.72 \text{ ng ml}^{-1}$ ), but did not alter adiponectin levels.<sup>16</sup> Furthermore, a review on pediatric obesity indicated that exercise has an impact on the adipose tissue and the release of adiponectin, resistin, and visfatin.<sup>17</sup> However, several studies also reported inconsistent results in the pediatric population.<sup>15</sup> Given this latter point we chose to carried-out a meta-analytic approach to examine the effects of exercise interventions compared with a control group on adipokines in overweight and obese youth. Our intent being to provide clarity on the role exercise plays in influencing the critical adipocytokines associated with obesity in a pediatric population.

## MATERIALS AND METHODS

The study was undertaken in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.<sup>18</sup> The review was registered with PROSPERO

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(CRD42016039025) at the University of York, United Kingdom. PROSPERO provides a comprehensive listing of systematic reviews registered at inception to help avoid unplanned duplication and enable comparison of reported review methods with what was planned in the protocol.

#### Literature search

Articles published before 10 May 2016, were retrieved by using searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (2002 to 10 May 2016), EMBASE (1980 to 10 May 2016) and MEDLINE (1965 to 10 May 2016) online databases. The search strategy included the topic's specialist journals. The search was conducted between the 1th and the 10th of May 2016. The terms used were: ('Obesity' and 'Overweight' OR), ('Exercise' and 'Training' and 'physical activity' and 'sport' OR). All Medical Subject Headings terms were combined with leptin\*, adiponectin\*, resistin\*, visfatin\*, adipokines\*, and publication type (randomized controlled trials [RCT]) as limiter. Also, the reference lists were examined to detect studies potentially eligible for inclusion. Studies reported in languages other than English were not explored.

#### Study selection and inclusion criteria

Two authors (RC and CP) independently screened the titles and abstracts of potentially eligible studies identified by the search strategy. Discrepancies between the two reviewers about study conditions were resolved by consensus with the third author (AG-H). The *a priori* inclusion criteria for this study were as follows: (a) children and adolescents classified as overweight or obese; (b) randomized controlled trials (RCT) studies in which the control group received no type of physical exercise or dietary restriction intervention; (c) interventions of supervised exercise (without hypocaloric diet intervention); and (d) evaluations of adipokines (adiponectin, leptin, resistin and/or visfatin).

#### Data collection

Two investigators (RC & CP) independently abstracted all data. Data were extracted regarding the year of publication, the characteristics of participants, exercise programs (type, frequency, duration and intensity), assessments and results. In cases in which duplicate research was published using the same population, the data from the study with the longest follow-up duration were used for the meta-analysis. A request asking for missing data was sent to each of the corresponding authors where appropriate.<sup>19</sup>

#### Risk of bias

Two investigators (RC and CP) independently performed the quality assessment. For the quality assessment of RCTs, we used the Delphi list as described by Verhagen *et al.*,<sup>20</sup> which includes eight questions with three response options 'yes', 'no', or 'do not know' depending on the compliance with key methodological components, and produces a quality score that provides an overall estimate of RCTs' quality.

#### Meta-analysis calculation

For the data analysis, we used Review Manager (Update Software, Oxford, UK) to calculate the weighted mean difference (WMD). The WMD of the adipokines from pre- to post-intervention between groups (exercise vs control)<sup>21</sup> in each study was calculated and pooled using the random effects model (DerSimonian–Laird approach). The underlying assumption of the random effects model is that samples are drawn from populations with different effect sizes, and that true effects differ between studies (that is, interventions, duration and so on).

#### Assessment of heterogeneity

The percentage of total variations across the studies due to heterogeneity (Cochran's Q-statistic)<sup>22</sup> was determined using  $I^2$ .  $I^2$  values of < 25, 25–50 and > 50% are considered to represent small, medium and large amounts of inconsistency.<sup>23</sup>

#### Publication bias and sensitivity

Each study was deleted from the model once in order to analyze the influence of each study on the overall results. The Egger test was used to examine publication bias.<sup>24</sup> In this case, the funnel plot test as a subsequent follow up was performed only in adiponectin due to in leptin and resistin the number of studies was less than the recommended arbitrary minimum number of ten studies.<sup>25</sup>

#### Meta-regression and subgroups analysis

The heterogeneity between studies using meta-regression was analyzed. We used covariates that may influence the association between exercise and adipokines: (a) total exercise program duration of each study (weeks); (b) frequency of sessions per week; (c) duration of exercise per session (minutes); and (d) changes in body fat (BF) post intervention. Also, subgroup moderator analyses were conducted to determine whether exercise effects differed according to intensity of the exercise (moderate, moderate-to-vigorous, and vigorous) according to American College of Sports Medicine cutoffs recommendations.<sup>26</sup>

## RESULTS

#### Study selection

The flow chart relative to data collection is shown in Figure 1. The literature search resulted in 733 studies. Titles and abstracts of returned articles were searched for suitability, leading to the retrieval of 44 full texts. Of those, 30 were rejected—23 for failing the study design criterion (no control group or RCT) and seven due to the type of intervention criterion (interventions with diet or no programmed exercise) (Supplementary Material 1). Finally, 14 RCTs met the inclusion criteria and were included in the meta-analysis.<sup>13,19,27–38</sup> In the included 14 trials, 5 RCTs analyzed leptin,<sup>19,30,31,34,36</sup> 10 analyzed adiponectin,<sup>13,28,29,31,32,34–36,38</sup> 2 analyzed resistin,<sup>31,36</sup> and only 1 visfatin.<sup>33</sup>

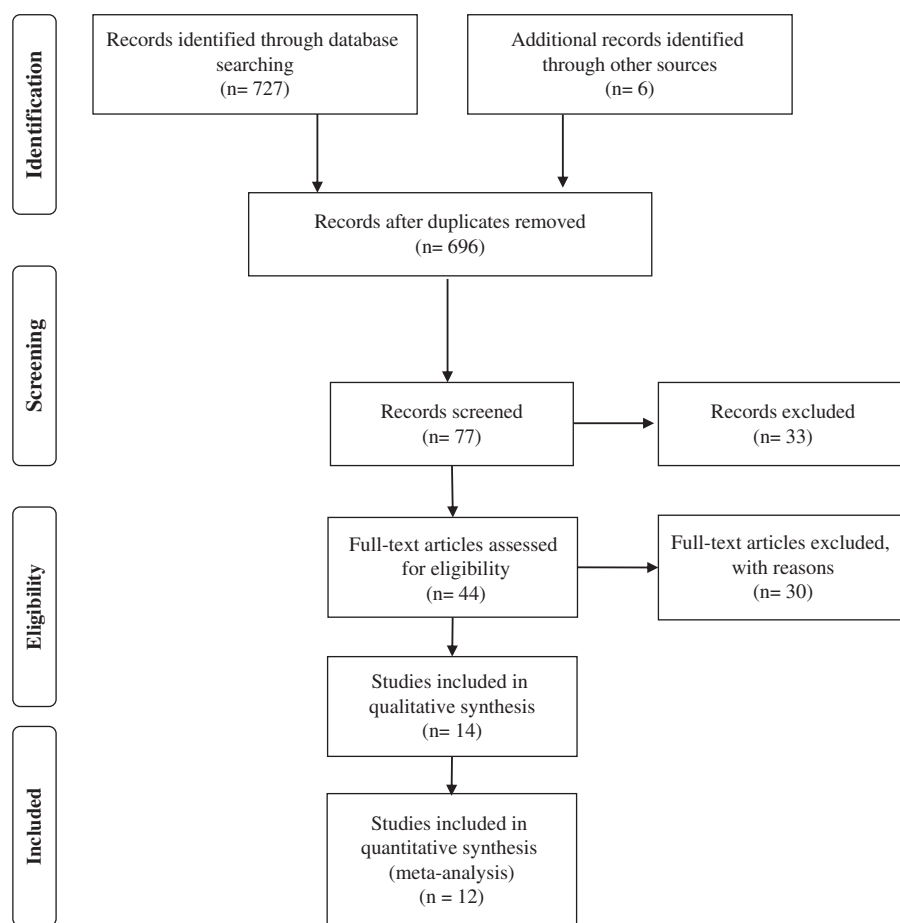
#### Description of the included studies

The characteristics of all included studies are shown in Table 1. The final analysis included a total of 347 youth (190 and 157 in exercise and control group, respectively). The youths were overweight/obese<sup>28,29,31,33,34,37</sup> or obese.<sup>13,19,27,30,35,36,38</sup> Three studies included only boys<sup>28,32,37</sup> and three only girls,<sup>33–35</sup> and the remaining studies included both boys and girls.<sup>13,19,27,29–31,36,38</sup> Participants in three studies were children (6–12 years old),<sup>28,29,31</sup> in eight adolescents (13–17 years old),<sup>13,19,32–38</sup> and in the other both age groups were included.<sup>27</sup>

The type of the programs was based on aerobic,<sup>30–33,35–37</sup> anaerobic<sup>35</sup> or aerobic plus resistance exercise.<sup>13,19,27,29,34,38</sup> The intensity of the exercise was moderate,<sup>29–32,35</sup> moderate-to-vigorous,<sup>28,34,36,38</sup> or vigorous<sup>35</sup> according to American College of Sports Medicine cut-offs recommendations.<sup>26</sup> Finally, adherence to the exercise programs was only reported in one study<sup>34</sup> (90%).

#### Risk of bias

Among the included studies, all satisfied four quality criteria: allocation randomized, inclusion criteria specified, baseline similar, and point estimate and variability (Supplementary Material 2).



**Figure 1.** Flow chart for identification of trials for inclusion in the meta-analysis.

#### Association of exercise intervention with adiponectin

Overall, exercise significantly increased adiponectin levels ( $n=10$  studies and 246 youths) by  $0.882 \mu\text{g/ml}$  (95% CI,  $0.271\text{--}1.493 \mu\text{g ml}^{-1}$ ,  $P=0.005$ ;  $I^2=23.3\%$ ; Figure 2). However, meta-regression analyses revealed a statistically significant relationship between adiponectin and change in BF ( $\beta=-0.072$ ; 95% CI,  $-0.173$  to  $-0.020$ ;  $P=0.013$ ), but not for the others covariates. Interestingly, in subgroup analyses, we observed a non-significant change in adiponectin levels for moderate-intensity exercise (WMD= $0.248 \mu\text{g ml}^{-1}$ ; 95% CI,  $-0.417$  to  $0.913 \mu\text{g ml}^{-1}$ ,  $P=0.465$ ;  $I^2=0\%$ ) and moderate-to-vigorous intensity (WMD= $0.745 \mu\text{g ml}^{-1}$ ; 95% CI,  $-0.519$  to  $2.010 \mu\text{g ml}^{-1}$ ,  $P=0.248$ ;  $I^2=0\%$ ).

#### Association of exercise intervention with leptin

Exercise non-significantly changed leptin levels ( $n=5$  studies and 94 youths) by  $-3.848 \mu\text{g ml}^{-1}$  (95% CI,  $-8.191$  to  $0.496 \mu\text{g ml}^{-1}$ ,  $P=0.083$ ;  $I^2=55.5\%$ ; Figure 2). Meta-regression analyses found statistically significant relationship between leptin, duration of the intervention ( $\beta=-0.708$ ; 95% CI,  $-1.276$  to  $-0.140$ ;  $P=0.014$ ), duration of the exercise per session ( $\beta=-0.156$ ; 95% CI,  $-0.297$  to  $-0.015$ ;  $P=0.030$ ), and change in BF ( $\beta=-0.729$ ; 95% CI,  $-1.374$  to  $-0.081$ ;  $P=0.027$ ). In subgroup analyses, we observed a significant change in leptin levels by moderate-intensity exercise (WMD= $-8.179 \mu\text{g ml}^{-1}$ ; 95% CI,  $-12.719$  to  $-3.640 \mu\text{g ml}^{-1}$ ,  $P<0.001$ ;  $I^2=0\%$ ), but not for moderate-to-vigorous intensity (WMD= $-0.758 \mu\text{g ml}^{-1}$ ; 95% CI,  $-5.953$  to  $4.438 \mu\text{g ml}^{-1}$ ,  $P=0.775$ ;  $I^2=18.7\%$ ).

#### Association of exercise intervention with resistin

Significant association was observed between exercise ( $n=2$  studies and 39 youths) and resistin levels by  $-0.611 \text{ng ml}^{-1}$  (95% CI,  $-3.463$  to  $2.242 \text{ng ml}^{-1}$ ,  $P=0.675$ ;  $I^2=0\%$ ; Figure 2). None of our covariates significantly explained our pooled analysis of resistin. Due to the limited number of studies, we did not conduct any subgroup analyses.

#### Publication bias and sensitivity analysis

Both funnel plot asymmetry and Egger test show no significant publication bias for adiponectin (Egger regression intercept,  $-3.55$  ( $P=0.015$ )) and leptin (Egger regression intercept,  $-0.42$  ( $P=0.381$ )). Due to limited number of studies, we did not conduct the Egger test for resistin.

Finally, in the sensitivity analysis, with each study removed from the model individually, the results remained constant across deletions.

#### DISCUSSION

The most prominent finding from this meta-analysis was that exercise training substantially increases adiponectin in childhood obesity. Also, exercise programs of longer duration as well as changes in BF seemed to favor a reduction in leptin levels. Similar conclusions have been reported in previous experimental studies<sup>29,31,34</sup> and narrative reviews.<sup>15,17</sup> Moreover, it is important to highlight that this is the first meta-analysis that has summarized the effectiveness of exercise training in modulating the adipokines

**Table 1.** Characteristics of the studies included in the meta-analysis

Study	EG		CG	BMI (percentile or $\text{kg m}^{-2}$ )	Intervention characteristics				Assessment		
	n	Age (years)			Type	n	Age (years)	Duration (weeks)		Frequency (Se/W)	Se duration (min)
Balogopal et al. <sup>19</sup>	8	15.6	Aerobic+Resistance	7	15.9	12	3	45	NR	NR	Leptin
Balogopal et al. <sup>13</sup>	8	15.6	Aerobic+Resistance	7	15.9	12	3	45	NR	NR	Adiponectin
Chae et al. <sup>27</sup>	19	10.4	Aerobic+Resistance	19	10.6	12	2	90	NR	NR	Adiponectin
Fazellifar et al. <sup>28</sup>	12	11-13	Aerobic+Resistance	12	11-13	12	3	10-30	50-85 HRmax	NR	Adiponectin
Jeon et al. <sup>29</sup>	8	11.0	Aerobic+Resistance	7	11.0	12	2	50	55-75 HRmax	NR	Adiponectin
Karacabey <sup>30</sup>	20	11.8	Aerobic	20	11.2	12	3	30-65	60-65 HRmax	NR	Leptin
Kelly et al. <sup>31</sup>	9	10.8	Aerobic	10	11.0	8	4	30	50-60 HRmax	NR	Leptin, Adiponectin, Resistin
Kim et al. <sup>32</sup>	14	17.0	Aerobic	12	17.0	6	5	40	NR	NR	Adiponectin
Kim et al. <sup>37</sup>	18	17.6	Aerobic	12	17.4	12	5	50	NR	NR	Adiponectin
Lee et al. <sup>33</sup>	11	16.9	Aerobic	7	16.9	12	3	30-40	60-80 HRmax	NR	Visfatin
Nunes et al. <sup>38</sup>	17	16.8	Aerobic+Resistance	8	15.4	24	4	60	60-100 VO2peak	NR	Adiponectin
Parik et al. <sup>34</sup>	15	12.1	Aerobic+Resistance	14	12.2	12	3	80	50-70 HRreserve	90	Leptin, Adiponectin
Racil et al. <sup>35</sup>	11	15.6	Aerobic	12	15.9	12	4	20	100-110 VO2peak	NR	Leptin, Adiponectin
Vasconcellos et al. <sup>36</sup>	11	16.3	Aerobic	10	14.8	12	3	60	70-80 VO2peak 84.8 HRmax	NR	Leptin, Adiponectin, Resistin

Abbreviations: CG, control group; EG, experimental group; HIIT, high-intensity interval training; HR, heart rate; MIIT, moderate-intensity interval training; NR, not reported; p, percentile; Se, session; W, week.

levels in pediatric obesity populations. However, the heterogeneity in the exercise programs (length of intervention, frequency, type of exercise and so on) and the limited number of youths could influence the final results, so we must carefully interpret these findings.

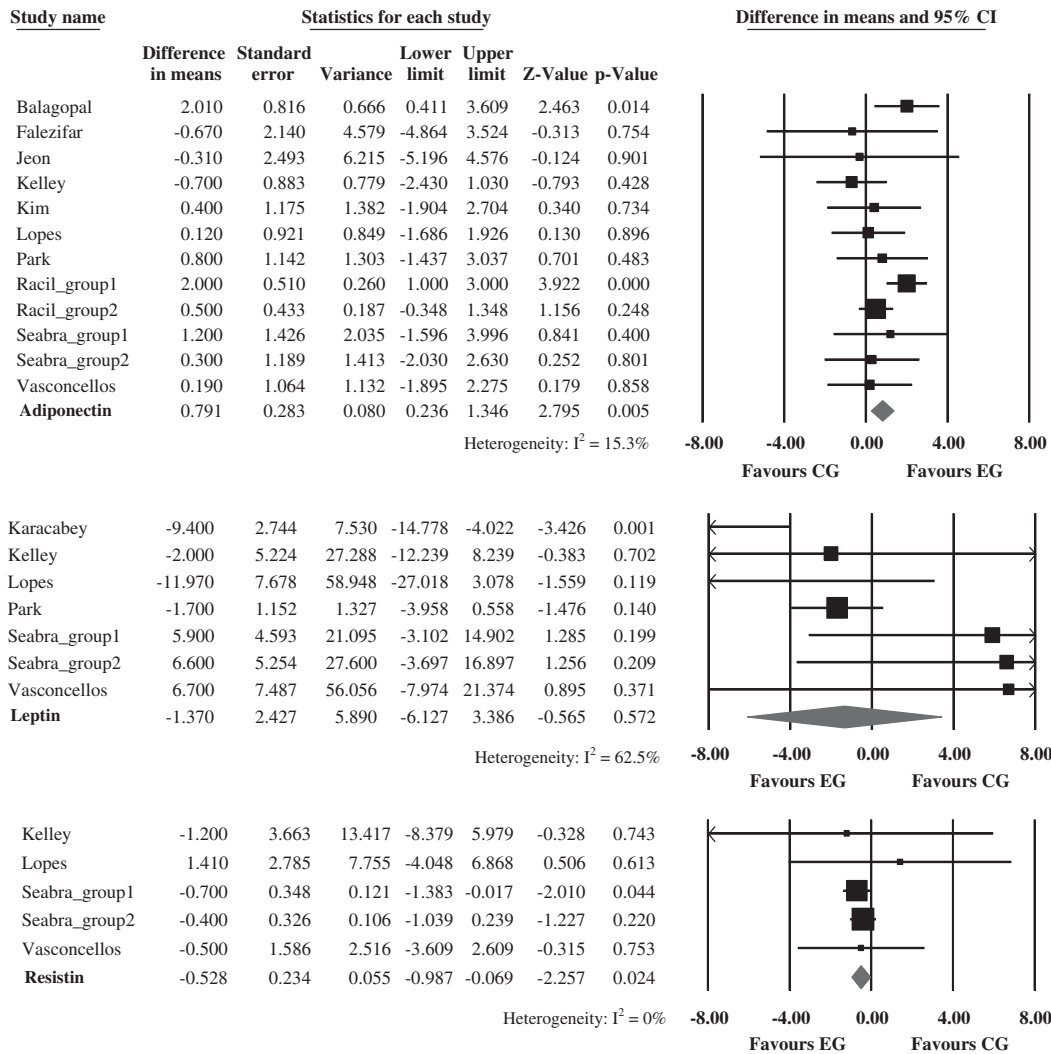
**Exercise may modulate adipokines levels in childhood obesity**

Most of the clinical recommendations for treatment of childhood obesity and its associated comorbidities are based on the combination of several interventions, such as changing eating habits, medication use, regular physical exercise and others items.<sup>39</sup> Thus, a number of studies have established an inverse relationship between the amount of physical activity or lifestyle intervention and increased release of pro-inflammatory adipokines by white adipose tissue in childhood obesity.<sup>40-42</sup> Likewise, exercise has been shown to be a safe and effective adjuvant therapy for influencing adiposity and overall body composition.<sup>15,17</sup> However, the role of different types of exercise in the specific reduction of the adipose tissue adipocytokines is unclear due to only a limited number of well-controlled long-term studies being available.<sup>41,43,44</sup> The type of exercise did not appear to affect any putative association; however, it is highly probable that different exercise modalities cause different responses in adipokines levels. Future research needs to address this point.

**Effects of exercise on adiponectin**

Adiponectin may be the most biologically active form regulating glucose homeostasis and evidence suggests that adiponectin is an important regulator of insulin sensitivity and glucose homeostasis.<sup>45</sup> Further studies suggested an inverse relationship between insulin resistance and type II diabetes with plasma adiponectin level.<sup>8</sup> In adults, a systematic review showed that exercise increases serum adiponectin, demonstrating small-to-moderate effect sizes.<sup>46</sup> The present meta-analysis confirm this adult study findings in childhood obesity; that is, showing a significantly increase of adiponectin levels. Therefore, there is some support for the use of physical exercise at an adequate duration and intensity to produce substantive changes in fitness levels and raise circulating adiponectin levels in children.<sup>15</sup> However, we also pooled data from non-RCT<sup>47-49</sup> and an increase was not observed in adiponectin levels (WMD = 0.483  $\mu\text{g ml}^{-1}$ , 95% CI, -0.527 to 1.493  $\mu\text{g ml}^{-1}$ ,  $P = 0.349$ ;  $I^2 = 0\%$ ).

In addition, our meta-regression analyses found a statistically significant relationship between adiponectin and change in BF ( $\beta = -0.097$ ), that is, exercise was more effective in influencing adiponectin in those children with a greater reduction in BF levels. This result was experimental showed recently by Lopes and colleges<sup>49</sup> in a RCT in thirty-three overweight girls, where a combined training program consisted of six resistance exercises (three sets of 6-10 repetitions at 60-70% 1 RM) followed by 30 min of aerobic exercise (walking/running) at 50-80%  $\text{VO}_{2\text{peak}}$  performed in the same 60 min session, 3 days/weeks, for 12 weeks. Dâmaso and colleges<sup>41</sup> showed a significant increase in adiponectin levels after 1 year of combined (aerobic plus resistance exercise) training included in a multidisciplinary program, possibly due to the significant reduction in body mass ( $\Delta = -12.3$  kg) and BF ( $\Delta = -14.2$  kg) found after the intervention. Our findings, consistent with these studies, were also observed by Nascimento and colleges<sup>47</sup> in a more recent non-RCT with a similar intervention using 5 h per week of moderate-to vigorous intensity physical exercise over eight weeks compared to a sedentary control group. Interestingly, these authors reported reductions in body mass index z-score and BF that were accompanied by an improvement in lipid profile and insulin resistance, a reduction in C-reactive protein, TNF-alpha, and an increase in adiponectin levels, suggesting a possible link between changes in adiponectin and body composition in pediatric overweight and obesity. Finally,



**Figure 2.** Absolute changes in adiponectin, leptin, and resistin levels in individual studies of exercise group vs control group. HIIT indicates High-Intensity Interval Training. MIIT indicates Moderate-Intensity Interval Training.

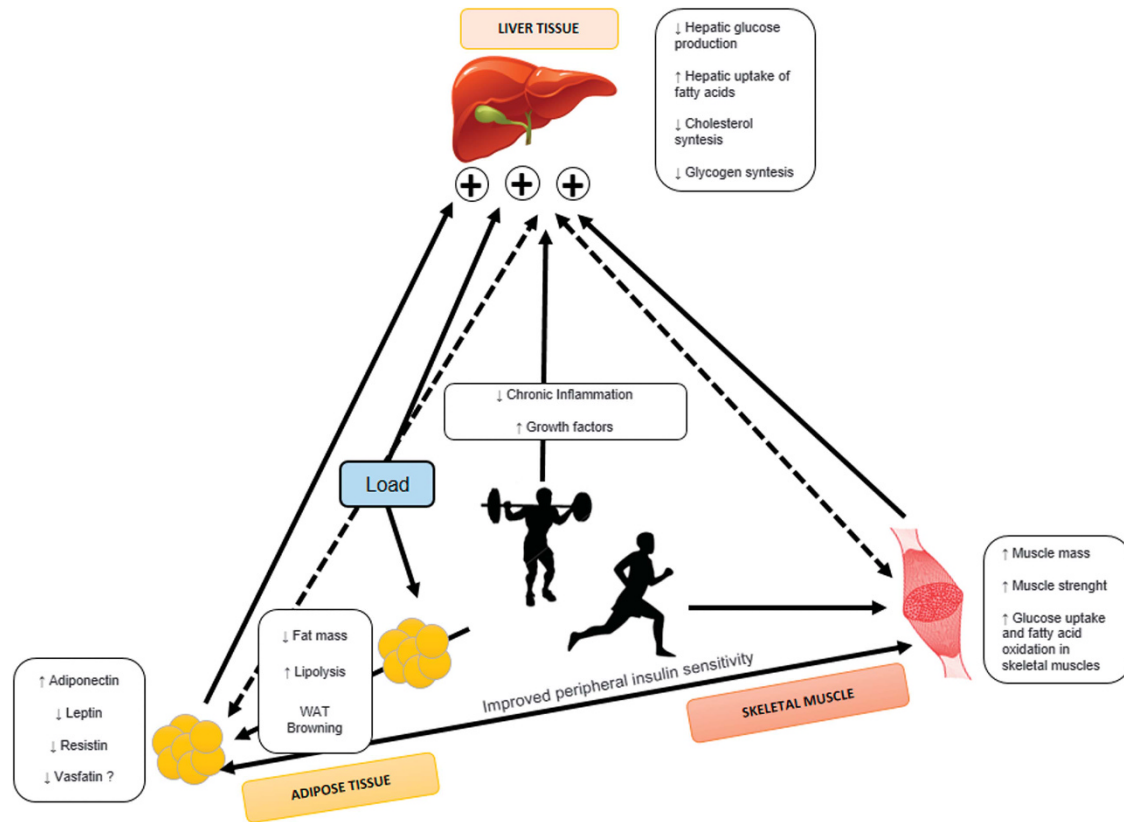
the greater increases observed in the Racil *et al.*<sup>35</sup> study, which analyzed 12-week interval training of high-intensity exercise in 34 adolescent females, highlighting the benefits of high-intensity interval exercise interventions in obese population.<sup>50</sup> In sum evidence suggests that adipokines are strongly correlated with BF<sup>51</sup> and that adequate amounts of exercise reduce BF,<sup>14</sup> therefore it is possible that any associations found in such an analysis would be due to decreases in BF alone.

#### Effects of exercise on leptin

Leptin is one of the best-known hormone markers for obesity and is very sensitive to levels of energy intake, particularly in energy deficient state.<sup>52</sup> Epidemiological studies indicate that increased leptin levels are associated with a higher frequency of adverse health consequences including obesity, systemic low-grade inflammation, and insulin resistance in obese youth.<sup>53,54</sup> Our pooled analysis demonstrated that exercise did not reduced leptin concentrations in childhood obesity. However, we pooled data from non-RCT<sup>47-49</sup> and observed a significant reduction in leptin levels (WMD = -5.537 µg/ml, 95% CI, -10.133 to -0.942 µg ml<sup>-1</sup>,  $P=0.018$ ;  $I^2=0\%$ ). Therefore, the evidence shows somewhat controversial results. For example, data from a Balagopal *et al.*,<sup>19</sup> confirm a decrease in leptin levels (from 22.1 ± 2.9 to 15.6 ±

2.0 ng/ml;  $P=0.001$ ) in response to lifestyle intervention, accompanied by decrease in fat mass further suggesting a potential role of the leptin-inflammatory axis in obese children. Recently, Lopes *et al.*<sup>49</sup> found a significant reduction in leptin (effect size: -0.95, 95% CI: -1.66 to -0.20  $P=0.001$ ) in overweight training after the experimental period. Another experimental therapy, regarding combined training as an adjuvant weight loss therapy for the treatment of chronic low-grade inflammation in obese adolescents, Dâmaso and colleges<sup>41</sup> found a significant reduction in leptin after 1 year of combined exercise training in obese adolescents. In contrast, no significant change leptin level could be detected by Vasconcellos *et al.*<sup>36</sup> after 12 weeks of a recreational soccer program in obese adolescents. The discrepancy between these results may be related to the type of the length of intervention (8 vs 12 vs 24 weeks) and design.

In addition, acute and short-term bouts of exercise do not appear to affect leptin levels. For example, short-term exercise (≤60 min), in obese females, walking at 60–80% of the heart rate maximum for 45 min did not alter leptin concentrations, although it decreased insulin resistance.<sup>55</sup> Contrastingly, longer durations of exercise (≥60 min) that are associated with increased energy expenditure (≥800 kcal) can decrease leptin concentrations.<sup>45</sup> This finding confirms our meta-regression analyses showing that



**Figure 3.** Exercise training–induced adipokines have an endocrine effect and improve whole-body metabolism. We propose a model whereby exercise causes release adipokines (decrease leptin and resistin, and increasing adiponectin), which can act in an endocrine manner to improve metabolism in skeletal muscle, white adipose tissue and liver.

duration of the intervention and duration of the exercise per session are negatively related to leptin levels.

On the other hand, an important point of interest in measuring leptin levels is paying attention to diurnal variations in its blood levels. Kraemer and colleagues<sup>56</sup> determined leptin levels in 15 healthy postmenopausal women at baseline, exercise, and recovery point intervals. Blood sampling with the same time intervals but without exercise was performed one month later as a control group. Even though no difference was detected between two groups, there was a gradual decrease from baseline levels to post-exercise and recovery period. Kraemer *et al.*<sup>56</sup> as well as Golbidi and Laher<sup>45</sup> emphasized the need to account for diurnal variations in measuring leptin levels over the course of exercise trials.

#### Effects of exercise on resistin

Resistin is produced by white and brown adipose tissues and is elevated in obesity.<sup>57</sup> It seems that resistin is involved in glucose homeostasis, lipid metabolism, and insulin action.<sup>58</sup> Our pooled analysis demonstrated that exercise not reduced resistin concentrations in pediatric obesity, confirming the existing dispute.<sup>31,59,60</sup> The small number of youths and studies included in the analysis could explain the non-significant effects. All of the RCTs had small sample sizes ( $n < 100$ ). Therefore, additional intervention on this topic is needed, including longitudinal interventions in this population and taking into account the limitations observed in this meta-analysis.

In contrast with the meta-analysis results, data from non-RCT<sup>47–49</sup> showed a significant decrease in resistin levels (WMD =  $-5.510 \text{ ng ml}^{-1}$ , 95% CI,  $-0.963$  to  $-0.058 \text{ ng ml}^{-1}$ ,  $P = 0.027$ ;  $I^2 = 0\%$ ). Specifically, Seabra *et al.*<sup>48</sup> showed a significant decrease in resistin levels (effect size:  $-0.22$  and 95% CI:  $-0.48$  to  $-0.91$ ) in 33 overweight girls (13–17 years). Also, data from the ACORDA

study<sup>47</sup> also confirm reductions; in this study, the authors found a 4% reduction in resistin in an intervention group composed of 117 overweight and obese children and adolescents that completed 5 h per week of moderate-to-vigorous intensity physical exercise during 8 weeks compared with a control group (that is, regular classes of physical education at school 3 times a week). Another consideration in assessing studies using an exercise intervention is the timing of blood sampling in relation to the exercise.<sup>61</sup> Most studies that have demonstrated a post-exercise increase in resistin found an immediate post-exercise spike followed by a gradual return to baseline or lower than baseline resistin levels over the next 30 min to several hours into recovery.<sup>62</sup>

#### Effects of exercise on visfatin

Visfatin is an adipokine that contributes to glucose and obesity-related conditions.<sup>63</sup> It is expressed in visceral adipose tissue and has been shown to exert insulin-mimetic effect. We found only one RCT that examined the effects of physical exercise on visfatin levels in obese female adolescents.<sup>33</sup> The results suggest that aerobic exercise resulting in an energy expenditure of 1,200–1,600 kcal per week for 12 weeks decreased plasma visfatin and insulin resistance. Another recent non-RCT suggests that regular exercise has positive effects on obesity in Korean children by improving glycemic control and reducing body weight, thereby lowering visfatin levels (from  $247.72 \pm 14.95$  to  $184.22 \pm 7.75$ ;  $P < 0.05$ ).<sup>60</sup> Congruent with these findings, Lai *et al.*<sup>64</sup> reported that a substantial decrease in HOMA-IR after exercise, might indicate that visfatin rs4730153 GG genotype (polymorphism), could possibly improve glucose metabolism in obese children and adolescents by enhancing insulin sensitivity to exercise. Due to the limited number of studies, ultimately, we did not conduct the meta-analysis on this hormone. Therefore, a greater number

of RCT studies are required to making safe conclusions as to what the effects of physical exercise would be on visfatin levels in childhood obesity.

#### Strengths and limitations

To our knowledge, this is the first meta-analysis that evaluates the changes on adipokines after exercise training in overweight and obese youths. Our results provide novel insight regarding the role of exercise as a non-pharmacological effective intervention in modulating the metabolic environment as well as in the management of childhood obesity. In addition, there were numerous methodological limitations that impacted the generalizability of studies, including a lack of adjustment for confounding factors (for example, plasma volume, participant age or body composition) and a lack of consideration of effect modification. Furthermore, our findings have crucial implications on interventional program in overweight/obese children and adolescents improved the adipokine profile, reducing pro-inflammatory molecules, such as leptin and resistin, and increasing adiponectin, important anti-inflammatory and anti-diabetic adipokines (Figure 3). In addition, all studies included exhibited moderate to high methodological quality and low risk of bias, which is an important issue in terms of external validity of our findings.

Nevertheless, there are some limitations with regard to our study exist that are important to state. The overall effects estimates were increased due to different modes of exercise across the studies included, although such differences were approached through subgroup analysis according to the mode of exercise. Statistical heterogeneity levels were detected for most of the effect estimates, which suggests some caution when interpreting our findings. This evidence of heterogeneity was counteracted by a random effects model of analysis and can be explained by differences in some characteristics of the exercise employed such as intensity, duration, intervention length, follow-up periods and adherence rates across studies. Finally, we must carefully interpret the findings due to the limited number of youths included in the meta-analysis and meta-regression.

In conclusion, our meta-analysis indicates that exercise was associated with increased adiponectin levels, while no significantly associations with leptin and resistin in overweight/obese children and adolescents were found. However, programs of longer duration as well as changes in BF seem favor a reduction in leptin levels. These findings will aid pediatricians and other health professionals with counseling patients and parents on physical activity and exercise prescription guidelines. Based on our results, we recommend exercise programs that involve both aerobic and resistance exercise on a regular basis, and that last longer than 24 weeks. Therefore, the data presented in this meta-analysis support current physical activity recommendations and suggest that physical exercise could be a critical strategy to control of obesity and inflammatory state progress in the pediatric population relative to some adipocytokines.

#### CONFLICT OF INTEREST

The authors declare no conflict of interest.

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