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Systematic Review

Does Physical Activity-Based Intervention Improve Systemic Proinflammatory Cytokine Levels in Overweight or Obese Children and Adolescents? Insights from a Meta-Analysis of Randomized Control Trials

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Keywords
Pediatric obesity · Exercise therapy · Adolescent · Exercise physiology · Inflammation mediators · Physical fitness

Abstract
Objectives: The purpose of this research was to conduct a meta-analysis of the role that physical activity (PA) plays in influencing the critical proinflammatory cytokine levels associated with overweight/obese children and adolescents to explore the effectiveness of exercise intervention within this population. ***Methods:*** With searches of the PubMed, EMBASE, and CENTRAL databases, we updated our meta-analysis up to November 2018. The randomized controlled trials (RCT) evaluated the ability of exercise training to increase the following factors in children and/or adolescents classified as obese or overweight: tumor necrosis factor (TNF)-α, interleukin (IL)-6, and C-reactive protein (CRP). ***Results:*** Eleven RCT comprising 623 children and/or adolescents who were obese or overweight (i.e., 393 with PA and 230 controls) were suitable for use in this study. The meta-analysis showed that PA in general was associated with a significant reduction of CRP levels (mean difference = −0.45 mg/L, $p = 0.02$) in overweight/obese children and adolescents. Based on 115 overweight and obese youths, this study suggests that PA does not significantly mitigate IL-6 levels (mean difference = −0.39 pg/mL, $p = 0.08$), although there was a trend towards a reduction. Additionally, no close connection was observed between PA and TNF-α levels at 0.04 pg/mL ($p = 0.78$). Moreover, meta-regression

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analysis revealed a statistical association between CPR levels and changes in BMI or changes in adiponectin; likewise, IL-6 levels dramatically impacted the effect of exercise on changes in adiponectin. ***Conclusions:*** PA was associated with significantly reduced CRP levels, whereas there was no significant association with IL-6 or TNF-α in overweight/obese children or adolescents; however, there was a trend towards a reduction of IL-6.

Introduction

The prevalence of childhood overweight or obesity has increased worldwide and constitutes a major public health crisis that brings about economic consequences and substantial healthcare costs [1–3]. Moreover, childhood obesity is associated with increased comorbidities, such as insulin resistance, diabetes mellitus, hypertension, sleep apnea, and cardiovascular disease [4–6], which also give rise to an increase in both direct and indirect costs [7]. Recently, the NCD Risk Factor Collaboration pooled population-based data from 1975 to 2016 to update the worldwide trends in pediatric obesity and showed that the increase in childhood and adolescent BMI has plateaued in high-income countries. However, some Asian countries have also demonstrated this plateau, albeit at high levels. Such trends are no longer correlated with those in adults [8]. For these reasons, avoiding obesity in childhood and identifying children with obesity and overweight problems at an early age, to begin intervention efficiently and maintain a healthy weight, is challenging and extremely urgent.

Lifestyle interventions for children and adults have included nutrition advice, regular exercise, and/or other weight loss programs. A recent meta-analysis suggested that a very large number of overweight or obese children and adolescents could benefit from lifestyle interventions [9]. Regarding the nutrition protocol, decreasing energy intake and/or increasing calorie expenditure has been adopted as a common method to promote weight loss [10]. Nevertheless, the results of the effects of increased physical exercise on weight still need further discussion, even though physical exercise has been acknowledged by scholars for decades as having beneficial effects, such as long-term protection against cardiovascular disease [11, 12]. However, physical activity (PA) seems to increase adiponectin levels but decrease resistin levels [13]. In reality, the function of PA in obesity treatment is too unclear for clinical practice [14].

During recent years, this protective impact has been associated with the modulation of inflammatory processes induced by exercise, as the risk of cardiovascular disease and chronic metabolic disease [12, 15] can be reduced through regular exercise, partially because anti-inflammatory effects are generated by exercise [16, 17]. There is an association between inflammatory cytokines and obesity in both adults and children, which suggests that there are some key inflammatory markers that have been consistently connected to both obesity and the risk of adverse outcomes in obesity-associated diseases [18]. For adults, chronic PA reduces serum inflammatory cytokine levels through multiple mechanisms, including decreases in proteic production by skeletal muscles [19], blood mononuclear cells [20], adipose tissue [21, 22], and endothelial cells [23], which can improve endothelial function and insulin sensitivity [22, 24]. In adolescents and children, the reported data tentatively suggest the ability of PA to reduce anti-inflammatory and proinflammatory cytokines [25–27]. Nevertheless, several studies have suggested that PA does not seem to decrease proinflammatory cytokine levels in overweight or obese children or adolescents [28, 29], although there are trends towards reductions in these cytokine levels in randomized controlled trials (RCT). Interestingly, the publication of results from a study of adolescent Korean girls with obesity shed light on exercise as a more effective method for improving the levels of serum

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proinflammatory cytokines, such as C-reactive protein (CRP) [30]. Thus, evidence of the effect of exercise on the control of inflammatory cytokine (pro- or anti-inflammatory) levels in overweight or obese children remains unclear.

Therefore, the purpose of this study was to conduct a meta-analysis of the studies on the role PA plays in modulating critical proinflammatory cytokine levels associated with overweight or obesity in children and adolescents to explore the effectiveness of exercise intervention within this population.

Materials and Methods

This study was undertaken based on the Cochrane Collaboration specified protocol (handbook version 5.1, available at http://handbook-5-1.cochrane.org/) and reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (available at http://www.prisma-statement.org/) [31].

Literature Search

A systematic literature search of relevant English articles on PA intervention and maintenance of usual activities (control) of children and adolescents who were overweight or obese was carried out using the MEDLINE database (PubMed) (1966 to November 2018), the EMBASE database (Embase) (1974 to November 2018), and the CENTRAL database (Cochrane Central Register of Controlled Trials) (2002 to issue 11 of 12, November 2018) by 2 independent researchers (Y.H. and Z.Z.). For the MEDLINE database search, the following Medical Subject Heading (MeSH) search terms were used: pediatric obesity, adolescent, exercise, randomized controlled trials as topic, and cytokines (online suppl. material; for all online suppl. material, see www.karger.com/doi/10.1159/000501970). In addition, exploded keywords included teen*, physical exercise*, and inflammatory*. For the EMBASE database search, the terms used were: randomized controlled trial, clinical trials as topic/exp, obesity/exp, overweight/exp, and PA. The CENTRAL database was explored using the following keywords: randomized controlled trials, clinical trials as topic, obesity, overweight*, PA, and exercise (online suppl. material). The research process was conducted between November 4 and 10, 2018. We limited our search to English language reports on human subjects. The relevant articles retrieved in this study were thoroughly checked in terms of their references. All literature was registered in the ISI Web of Knowledge: Web of Science database (1991–2018), through which articles being cited can be found.

Selection

RCT studies were used only if the following inclusion criteria were met: (a) The children and adolescents were classified as overweight or obese; (b) the individual intervention protocol was premeditated PA (without any dietary intervention); and (c) the study contained sufficient data (at least one proinflammatory cytokine) on factors such as hsCRP, IL-2, IL-6, IL-8, and TNF-α.

In cases of multiple reports from the same institution, only the published report with the most details was included to prevent data duplication.

Articles were excluded if it they: (a) did not report outcomes in a comparable fashion, such as with comparisons to a lean group; (b) allowed another kind of physical exercise or dietary restriction intervention to be received by the control group; (c) contained insufficient data (no proinflammatory cytokines); or (d) failed to satisfy the standards for unpublished data and abstracts.

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Assessment of Risk of Bias

The quality evaluation was conducted by 2 investigators (Y.H. and S.Z.) independently. Trials were included by methodological quality, which was evaluated with the Cochrane Collaboration tool [32]. The method consists of the following items: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), incomplete outcome data (attrition bias), and selective reporting (reporting bias). The evaluation of unclear, low- or high-risk of material bias was made for each item according to the Cochrane Collaboration handbook (version 5.1).

Data Abstraction

After the initial assessment for eligibility, 2 of the authors (Y.H. and Y.L.) independently conducted the data extraction from the primary sources, and they independently reviewed all of the articles. Any differences in results between the 2 authors were resolved by consensus. For each study, we extracted rudimentary information that included: author, date published, PA group protocol (type, frequency, duration, and intensity), proinflammatory cytokines reported, and control group protocol. Moreover, proinflammatory cytokine levels before and after the intervention period were specifically recorded. Indispensably, requests for missing or incomplete data were sent to every corresponding author.

Quantitative Data Synthesis

First, we calculated the individual changed score in the weighted mean difference with the 95% CI from pre- to postintervention between groups for proinflammatory cytokine levels using a method described by Morris [33]. Furthermore, the weighted mean difference was calculated as the sum of the difference in mean proinflammatory cytokine levels before and after the intervention between groups (PA vs. control). Finally, we performed a meta-analysis of proinflammatory cytokine levels using the formula for SEM to represent the SD through the square root of the sample size with the aim of pooling data.

Assessment of Heterogeneity

This study adopted the fixed effects model unless evidence of significant heterogeneity was found. The degree of heterogeneity was assessed using the I^2 test. I^2 values of 25, 25–50, and >50% were considered to represent small, medium, and large amounts of inconsistency [34].

Publication Bias Assessment

Publication bias was detected using a funnel plot. The data points were distributed symmetrically and shaped like an inverted V when no publication bias was present. Furthermore, to evaluate heterogeneity, the data points were used to form the Egger regression asymmetry plot [35], and Egger graphical exploration was used to assess publication bias [36].

Meta-Regression Analysis

This study also presents an analysis of the heterogeneity between studies. The following covariates, which might impact the association of proinflammatory cytokines and exercise, were used: (a) duration of exercise in each study (weeks); (b) frequency of sessions per week; (c) duration of exercise per session (min); (d) changes in body composition after the intervention; (e) changes in lipoprotein; (f) changes in insulin resistance; (g) changes in blood pressure; and (h) changes in adipokines, such as adiponectin.

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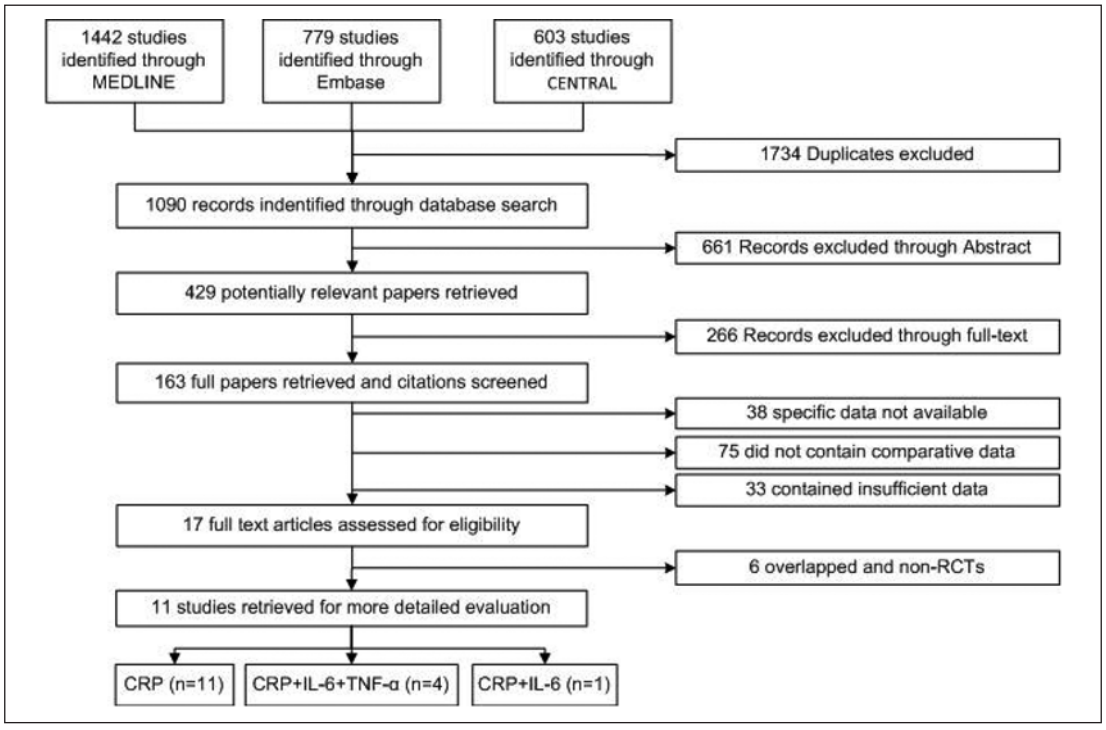

Fig. 1. PRISMA 2010 flow diagram.

Statistical Analysis

$p < 0.05$ was considered statistically significant. A spread sheet was used to conduct all statistical analyses (Microsoft Excel 2010; Microsoft, Redmond, WA, USA), and risk-of-bias assessments, data synthesis, and funnel plots were carried out with Review Manager (version 5.3, available at http://community.cochrane.org/tools/review-production-tools/revman-5/revman-5-download). Due to statistical software uniqueness and functionality, meta-regression and the Egger test/Egger plot were carried out using the meta.ado module of statistical software-STATA (version 12.0; College Station, TX, USA).

Results

Trial Flow

The literature search identified 163 studies for potential inclusion in the meta-analysis; 146 papers were excluded, 38 studies reported specific data that were not available, 75 did not contain comparative data, and 33 contained insufficient data. Another 17 papers were further assessed for eligibility. Of these, 4 papers overlapped with included studies from the same 2 datasets [37–40] and 4 individuals and did not meet the study design criteria (non-RCT) [41–44]. The trial flow charts for how these were obtained are provided in Figure 1.

Studies Selected

Table 1 presents the details of the selected articles used in this study. These articles consisted of 11 RCT: 6 independent reports of CRP [28, 30, 45–48], 1 study of CRP and IL-6 [37], and 4 studies of CRP, IL-6, and TNF-α [29, 39, 49, 50]. Two studies included a population of boys only [48, 50], 1 study reported on only girls [30], and 8 studies included both boys

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Table 1. Summary of the included studies

Authors	Year	Country	BMI	Patients, *n*	Males, *n*	Age, years	Intervention	Intervention duration	Bouts/ frequency	Session duration	Intensity	Recovery	Controls, *n*	Males, *n*	Age, years	Program
Vasconcellos et al. [49]	2016	Brazil	>2 SD	10	8	14.1±1.3	small pitch game (soccer)	12 weeks	3 days per week	40 min	NG	10 min cool-down	10	6	14.8±1.4	NG
Alberga et al. [45]	2015	Canada	≥85th percentile	75	22	15.5±1.4	aerobic training	22 weeks (range 5–26)	NG	20–40 min	70–85% HRmax	NG	76	24	15.6±1.3	postponed exercise
				78	23	15.9±1.5	resistance training	22 weeks (range 5–26)	2–3 sets	6–15 repetitions	NG	NG				
				75	22	15.5±1.3	combined	22 weeks (range 5–26)	4 days per week	NG	NG	NG				
Park et al. [46]	2012	South Korea	≥85th percentile	15	7	12.1±0.1	after-school exercise	12 weeks	3 days per week	80 min	60–70% HRmax	10 min cool-down	14	7	12.2±0.1	maintain activities
Balagopal et al. [38]	2010	USA	NG	8	4	15.6±0.3	aerobic activities (brisk walking)	3 months	3 days per week	45 min		5 min slow walking	7	4	15.9±0.5	given advice
Farpour-Lambert et al. [47]	2009	Switzerland	97th percentile	22	13	9.1±1.4	aerobic+ strengthening exercises	3 months	3 days per week	60-min sessions/week after school	55–65%	10 min stretching	22	15	8.8±1.6	maintain usual activities
Murphy et al. [29]	2009	USA	≥85th percentile	23	NG	7–12	Dance Dance Revolution	12 weeks	5 days per week	10→15→20→ 25→30 min	NG	NG	12	NG	7–12	NG
Wong et al. [48]	2008	Singapore	≥25th percentile	12	12	13.75±1.06	aerobic+strength+ resistance+game	12 weeks	2 days per week	45–62, 55 min on average	65–85%	7–10 min cool-down	12	12	14.25±1.54	NG
Kim et al. [50]	2007	South Korea	NG	14	NG	17±0.11	jump roping	6 weeks	5 days per week	40 min	NG	5 min cool-down, stretching	12	NG	17±0.11	physical education class
Kelly et al. [39]	2007	USA	>85th percentile	9	4	10.8±0.67	stationary cycling	8 weeks	4 days per week	30→40→50 min	50–60% HRmax	5 min cool-down	10	4	11.0±0.71	NG
Park et al. [30]	2007	Republic of Korea	NG	19	0	14.2±0.5	lifestyle education+ training (walking)	12 weeks	6 days per week	10 min in the morning+30–40 min in the afternoon	55–75% HRmax	NG	21	0	14.1±0.5	maintain their lifestyle
Meyer A et al. [28]	2006	Germany	≥97th percentile	33	17	13.7±2.1	aerobic+sports games+walking	6 months	3 days per week	60+90+60 min	NG	NG	34	17	14.7±2.2	maintain current PA

HRmax, maximum heart rate; NG, not given.

Table 2. Baseline and postintervention changes in serum CPR level between OE youths and OC youths

Study	Year	CRP at baseline, mg/dL						CRP postintervention, mg/dL					
		OE, *n*	OE (mean)	OE (SD)	OC, *n*	OC (mean)	OC (SD)	OE, *n*	OE (mean)	OE (SD)	OC, *n*	OC (mean)	OC (SD)
Vasconcellos et al. [49]	2016	10	4.3	3.2	10	3.9	1.3	10	3.7	1.8	10	4.1	2.3
Alberga et al. [45] (aerobic)	2015	75	2.61	2.86				55	2.23	2.37			
Alberga et al. [45] (resistance)	2015	77	2.64	2.89	76	2.24	2.44	50	2.26	2.33	56	1.98	2.10
Alberga et al. [45] (combined)	2015	75	1.95	2.17				58	1.9	2.06			
Park et al. [46]	2012	15	1.6	1.55	14	1.9	2.62	15	1.4	1.16	14	0.7	0.37
Balagopal et al. [38]	2010	8	3.11	1.92	7	3.95	3.07	8	2.22	1.47	7	6.72	5.50
Farpour-Lambert et al. [47]	2009	22	3.57	5.57	22	4.94	4.41	22	3.43	3.67	22	4.76	3.21
Murphy et al. [29]	2009	23	3.1	2.9	12	4.7	2.7	23	2.6	7.1	12	4.8	2.6
Wong et al. [48]	2008	12	3.1	1.4	12	3.4	2.4	12	4.1	5.0	12	4.3	3.5
Kelly et al. [39]	2007	9	4.4	4.8	10	5.0	3.79	9	4.8	7.8	10	3.8	2.85
Kim et al. [50]	2007	14	1.7	1.87	12	0.9	2.43	14	1.0	2.46	12	2.1	2.43
Park et al. [30]	2007	19	1.0	1.0	21	0.8	0.5	19	0.9	0.7	21	1.1	0.8
Meyer et al. [28]	2006	33	4.84	6.31	34	4.61	0.54	33	2.05	2.44	34	3.36	4.76

OE, obesity/overweight exercise; OC, obesity/overweight control.

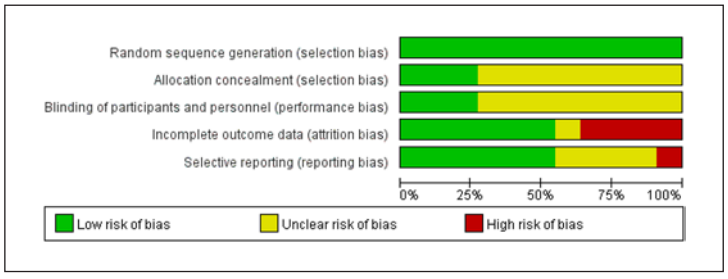

Fig. 2. Study risk of bias in this meta-analysis.

and girls [28, 29, 37, 39, 45–47, 49]. The articles were published from 2005 to 2016 and consisted of 5 from North and South America, 2 from Europe, and 4 from Asia.

Risk of Bias Assessment

The data (Fig. 2, 3) showed that 3 RCT studies adequately met all of the methodological requirements of the Cochrane risk-of-bias tool; 6 were considered to be at a low risk of bias, and the remaining trial was graded as moderate risk.

Quantitative Data Synthesis

Main Results

Exercise intervention and CRP in both adolescents and children who suffered from obesity problems were evaluated. The unit of measurement for CRP assessment varied as follows: milligrams/milliliter [50], milligrams/deciliter [46, 49], milligrams/liter [28, 30, 38, 39, 45, 48], micrograms/milliliter [28] and millimoles/liter [47], respectively. Table 2 lists the values for each serum CRP level in all studies before and after the intervention. Overall, PA significantly decreased serum CRP levels (n = 11 studies and 430 youths) by –0.45 mg/L (95% CI –0.81 to –0.08 mg/L, p = 0.32, I^2 = 13%) in overweight and obese children and adolescents (Fig. 4a). Publication bias was also evaluated with a funnel plot of all studies reporting on the CRP level after exercise, and it demonstrated that all points were within the trilateral region. Interestingly, meta-regression analysis indicated that there was a close association

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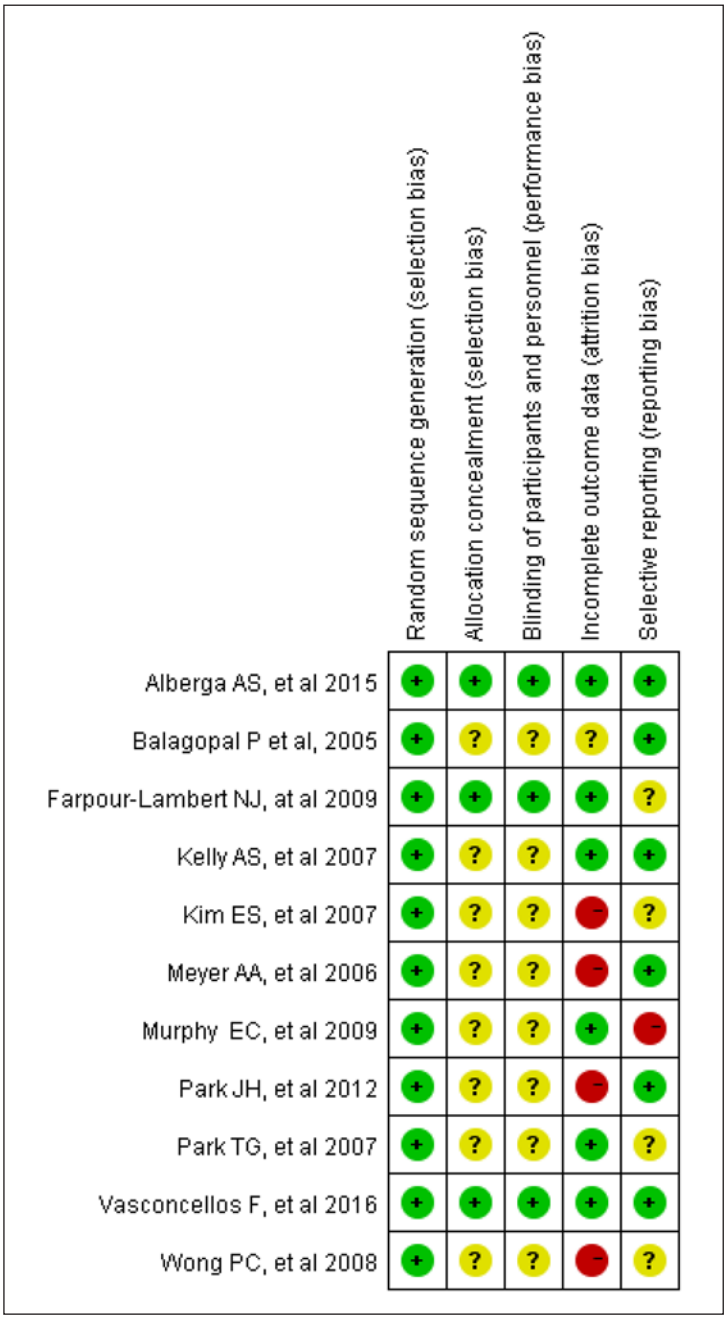

Fig. 3. Reviewers' judgements about each methodological quality item in the included studies. A dot with a plus sign indicates that the item was fulfilled for this study, a dot with a question mark indicates that this item was unclear in this study, and a dot with a minus sign indicates that this study did not fulfil this item.

between changes in BMI and CPR levels (β = 0.205; 95% CI 0.038–0.421, $p = 0.023$). Moreover, changes in adiponectin negatively predicted the observed improvements in CRP levels (β = –0.218; 95% CI –0.404 to –0.029, $p = 0.0017$) but not in the other covariates.

Exercise intervention and IL-6 in both adolescents and children suffering from obesity problems were evaluated. Of the 11 included trials, 5 RCT analyzed IL-6 levels, and the unit of measurement varied as follows: picograms/milliliter [29, 39, 49, 50] and milligrams/milliliter [38]. Based on an analysis of 115 youths who were overweight or obese (Table 3), our results suggested that PA did not significantly mitigate the serum IL-6 levels (mean difference = –0.50 pg/mL, 95% CI –1.41 to 0.40 pg/mL, $p = 0.28$, $I^2 = 53\%$), although there was a trend toward a reduction (Fig. 4b). Funnel plot asymmetry showed no significant publica-

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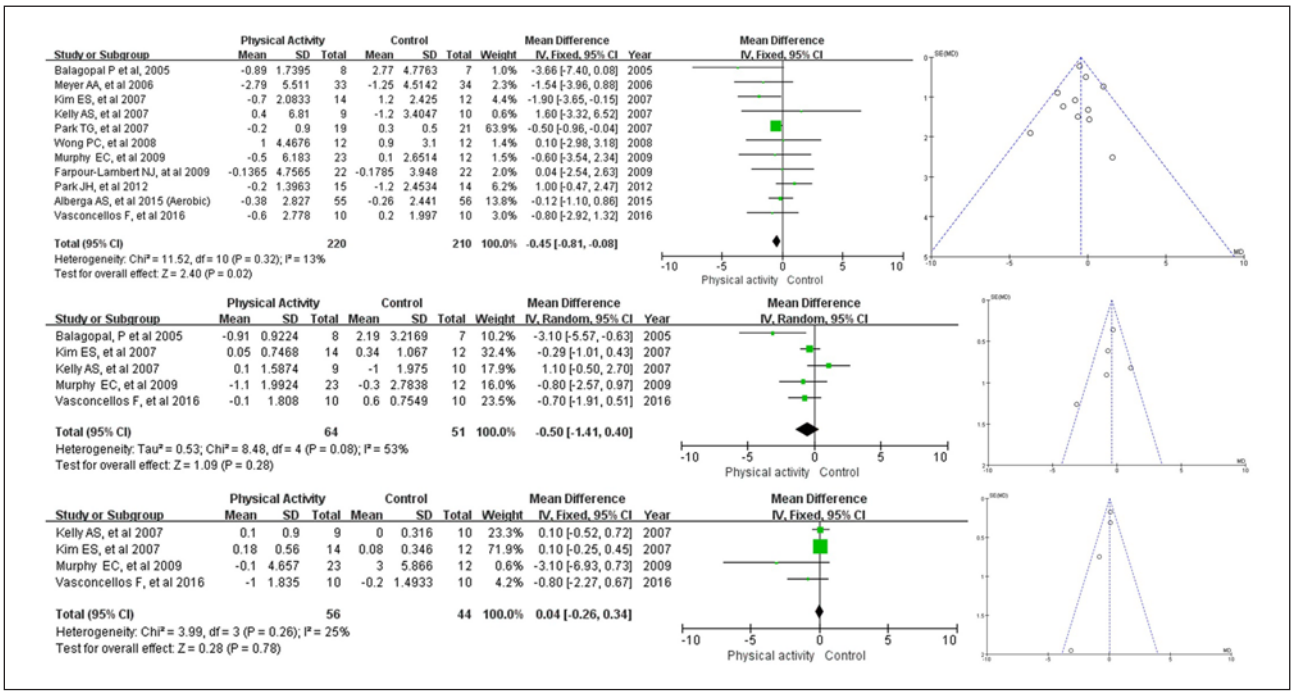

Fig. 4. Absolute changes in CRP (upper panel), IL-6 (middle panel), and TNF-α (bottom panel) in individual studies of the exercise group vs. the control group in obese or overweight children and adolescents.

Table 3. Baseline and postintervention changes in serum IL-6 levels between OE youths and OC youths

Study	Year	IL-6 at baseline, pg/mL						IL-6 postintervention, pg/mL					
		OE, *n*	mean	SD	OC, *n*	mean	SD	OE, *n*	mean	SD	OC, *n*	mean	SD
Vasconcellos et al. [49]	2016	10	2.2	1.7	10	1.7	0.7	10	2.1	1.9	10	2.3	0.8
Murphy et al. [29]	2009	23	3.6	2.3	12	4.6	3.0	23	2.5	1.2	12	4.3	2.5
Kelly et al. [39]	2007	9	2.2	1.2	10	3.5	2.2	9	2.3	1.8	10	2.5	1.58
Kim et al. [50]	2007	14	0.67	0.37	12	0.53	0.17	14	0.72	0.86	12	0.87	1.14
Balagopal et al. [37]	2005	8	3.96	0.88	7	4.42	1.11	8	3.05	0.96	7	6.61	3.63

OE, obesity/overweight exercise; OC, obesity/overweight control.

Table 4. Baseline and postintervention changes in serum TNF-α level between OE youths and OC youths

Study	Year	TNF-α at baseline, pg/mL						TNF-α postintervention, pg/mL					
		OE, *n*	mean	SD	OC, *n*	mean	SD	OE, *n*	mean	SD	OC, *n*	mean	SD
Vasconcellos et al. [49]	2016	10	3.1	2.1	10	2.7	1.1	10	2.1	0.8	10	2.5	1.7
Murphy et al. [29]	2009	23	11.3	4.8	12	11.1	6.1	23	11.2	4.5	12	11.1	6.1
Kelly et al. [39]	2007	9	1.3	0.3	10	1	0.1		1.4	0.3	10	1	0.1
Kim et al. [50]	2007	14	1.75	0.15	12	1.68	0.1	14	1.93	0.16	12	1.76	0.1

OE, obesity/overweight exercise; OC, obesity/overweight control.

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Table 5. Effects of OE intervention compared to OC intervention on body composition, lipid metabolism marker, cardiometabolic risk factors, and insulin resistance in children or adolescents

Parameter	Studies, *n*	OE, *n*	OE baseline		OE postintervention		OC, *n*	OC baseline		OC postintervention		MD	95% CI (lower)	95% CI (upper)	I^2, %	*p* value
			mean	SD	mean	SD		mean	SD	mean	SD					
BMI	9	157	28.98	4.13	28.01	3.91	147	29.48	4.23	29.69	3.97	−1.394	−2.074	−0.715	0.0	<0.001
Weight, kg	8	117	77.99	13.14	76.59	12.03	106	80.56	17.05	82.19	16.55	−3.176	−6.156	−0.195	0.0	0.037
Fat, %	7	119	39.73	5.95	38.21	5.99	121	39.93	5.71	39.70	5.86	−1.951	−3.421	−0.481	0.0	0.009
Fat-free mass, kg	3	44	40.67	6.83	42.20	6.13	44	41.47	8.07	42.50	8.27	1.047	−1.373	3.466	0.0	0.397
Waist, cm	4	53	89.98	7.98	85.48	7.59	55	89.48	9.07	89.25	8.64	−4.282	−7.061	−1.504	0.0	0.003
SBP, mm Hg	8	148	121.38	10.50	116.85	10.18	137	122.01	10.04	121.68	9.29	−4.101	−7.521	−0.680	51.4	0.019
DBP, mm Hg	7	115	73.34	6.62	72.06	8.43	103	74.34	7.07	72.80	6.86	−0.498	−2.397	1.400	0.0	0.607
Total cholesterol, mg/dL	7	115	164.76	28.49	160.22	28.77	103	167.87	26.33	169.75	27.05	−6.875	−14.186	0.437	13.5	0.065
HDL, mg/dL	8	148	43.15	8.76	45.45	8.44	137	42.67	10.78	43.59	8.40	0.608	−1.438	2.653	0.0	0.560
LDL, mg/dL	8	148	102.4	26.03	99.67	23.22	137	106.15	25.94	107.86	25.16	−5.237	−11.138	0.663	0.0	0.082
Triglyceride, mg/dL	8	148	100.35	59.77	87.95	37.49	137	96.92	47.86	104.09	46.01	−16.457	−27.611	−5.302	0.0	0.004
Fasting blood glucose, mmol/L	7	115	4.82	0.41	4.79	0.37	103	4.85	0.36	4.93	0.44	−0.077	−0.252	0.099	61.0	0.392
Serum insulin, μU/mL	7	126	12.62	5.89	11.55	5.34	115	13.43	6.24	14.70	8.39	−1.536	−3.049	−0.023	40.8	0.047
Adiponectin, μg/mL	7	98	8.25	2.70	8.84	3.23	86	7.77	2.29	7.74	2.55	0.592	−0.177	1.361	0.0	0.131

OE, obesity/overweight exercise; OC, obesity/overweight control.

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Table 6. List of publication bias evaluated using a funnel plot and the Egger test

Parameter	Studies, *n*	Funnel plot	Egger regression intercept	Egger test
CRP, mg/L	11	–	–0.151	0.778
IL-6, pg/mL	5	–	–1.174	0.541
TNF-α, pg/mL	4	?	–1.024	0.259
BMI	9	–	0.32	0.537
Weight, kg	8	–	0.056	0.904
Fat, %	7	+	2.536	0.018
Fat-free mass, kg	3	?	–0.499	0.021
Waist, cm	4	–	0.202	0.877
SBP, mm Hg	8	–	0.187	0.942
DBP, mm Hg	7	?	1.727	0.199
Total cholesterol, mg/dL	7	–	0.303	0.891
HDL, mg/dL	8	?	1.286	0.104
LDL, mg/dL	8	–	0.935	0.551
Triglyceride, mg/dL	8	–	–0.976	0.362
Fasting blood glucose, mmol/L	7	?	–2.017	0.293
Serum insulin, μU/mL	7	–	–1.336	0.526
Adiponectin, μg/mL	7	–	–0.144	0.946

tion bias for a change in IL-6 level. Furthermore, metaregression analysis showed a statistically significant relationship between a change in IL-6 and a change in adiponectin (β = –0.404; 95% CI –0.709 to –0.200, $p = 0.029$) but no relationship with the other covariates.

Exercise intervention and TNF-α in both adolescents and children suffering from obesity problems were evaluated. As shown in Table 4, there was no close correlation between PA ($n = 4$ studies and 100 children and adolescents) and TNF-α levels at 0.04 pg/mL (95% CI –0.26 to 0.34 pg/mL, $p = 0.78$, $I^2 = 25\%$), although there was a trend toward an increase (Fig. 4c). As the number of studies was limited, we did not perform a meta-regression analysis for TNF-α.

Secondary Results

The results of this meta-analysis revealed a significant mean effect of exercise intervention on reducing the body composition as follows: BMI by –1.394, weight by –3.176 kg, percent body fat by –1.951, and waist circumference by –4.282 cm. However, the results suggest a nonsignificant trend towards an increase in fat-free mass (mean difference = 1.047 kg, $p = 0.397$) following exercise. Significant differences between the PA and the control groups of overweight or obese youths were observed for systolic blood pressure (mean difference = –4.101 mm Hg, 95% CI –7.521 to –0.680 mm Hg, $p = 0.019$) but not for diastolic blood pressure. Moreover, exercise did not significantly change traditional lipid-related biomarkers, such as total cholesterol, HDL, or LDL, but it did change triglyceride levels (mean difference = –16.457 mg/dL, $p = 0.004$). There was also a nonsignificantly greater improvement in fast glucose and serum adiponectin levels, but PA was associated with reductions in fasting insulin levels by –1.536 μU/mL ($p = 0.047$). All secondary outcomes are summarized in Table 5.

Publication Bias

First, publication bias was evaluated with a funnel plot of all analyses reporting on dominant results, such as CRP, IL-6, and TNF-α, and the secondary results in Table 6, which demonstrated that most of the points were within the trilateral region. Furthermore, publication bias was evaluated using the Egger test (results in Table 6), and the plot shows that the regression line passes through the point of origin, which may indicate the absence of bias, except for fat percent and fat-free mass.

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Discussion/Conclusion

The number of systematic reviews and meta-analyses that have reported, either qualitatively or quantitatively, serum inflammatory cytokine trends in adults suffering from obesity and overweight problems after PA and in obese children or adolescents is limited. To our knowledge, the present study is the first meta-analysis to compare the effectiveness of exercise interventions to that of control interventions for improving proinflammatory cytokines in overweight or obese children and adolescents. In this study, the meta-analysis showed that PA significantly decreased serum CRP levels in overweight or obese children and adolescents. The meta-regression suggested a significant negative relationship between CRP levels and a changes in adiponectin. Moreover, although there was a trend toward a reduction, our results showed no significant association between PA and either TNF-α levels or IL-6 levels.

Statistical Performance of This Meta-Analysis

For a meta-analysis, heterogeneity is the major concern. However, during this research, there was little evidence of heterogeneity, which partially demonstrated why a well-done randomized controlled study design was adopted. To acquire a higher statistical effectiveness and more accurate conclusions, such as in the study of Alberga et al. [45], we extracted individual serum CRP levels from 3 different exercise groups (aerobic training, resistance training, and combined aerobic and resistance training) as well as from a nonexercising control group. Corresponding data from 3 different exercise intervention groups were analyzed with RevManager and, as expected, the subgroup analysis (online suppl. material) did not change our conclusions. Moreover, because Kelly et al. [40], Kelly et al. [39], Balagopal et al. [37], and Balagopal et al. [38] reported from the same institution, they were treated as one study for the purpose of this analysis. The former data were replenished with the latter and, consequently, all data were fitted into our study.

Five Possible Mechanisms

Additional adipose tissue underlies the problem of obesity and overweight in children and adolescents. White adipose tissue also functions as a type of endocrine organ that can lead to energy homeostasis [51]. Thus, macrophages that infiltrate white adipose tissue in obesity are responsible for the regulation of the adipose tissue's inflammatory state [18, 52], and the expansion of white adipose tissue leads to the increased generation of proinflammatory adipokines, such as TNF-α, leptin, IL-6, and IL-18 [51]. Conversely, the specific number of anti-inflammatory cytokines, such as adiponectin, is decreased [51]. Simultaneously, IL-6 is a powerful inducer of the hepatic acute phase response, which leads to increased concentrations of acute phase reactants, such as CRP [22, 53].

The decreased levels of proinflammatory cytokines after exercise intervention in youths may be due to 5 distinct mechanisms. First, PA might improve inflammatory cytokines by reducing the visceral fat mass. Through regular exercise, people can decrease their BMI, fat percentage and waist circumference, with consequently large decreases in abdominal and visceral fat mass; this was also observed in our meta-analysis. Indeed, this meta-regression analysis revealed a statistically significantly positive relationship between the CPR level and a change in BMI. Moreover, exercise might elevate anti-inflammatory cytokines, such as adiponectin. Weight loss improves inflammation in terms of anti-inflammatory cytokines (adiponectin) [51, 54], and this was also observed in our meta-analysis, suggesting a significantly negative relationship between CPR levels and changes in adiponectin by meta-regression. Furthermore, PA may also alter macrophage activation, resulting in an inflammatory cytokine level. M1-type macrophages produce nitric oxide, IL-6, and

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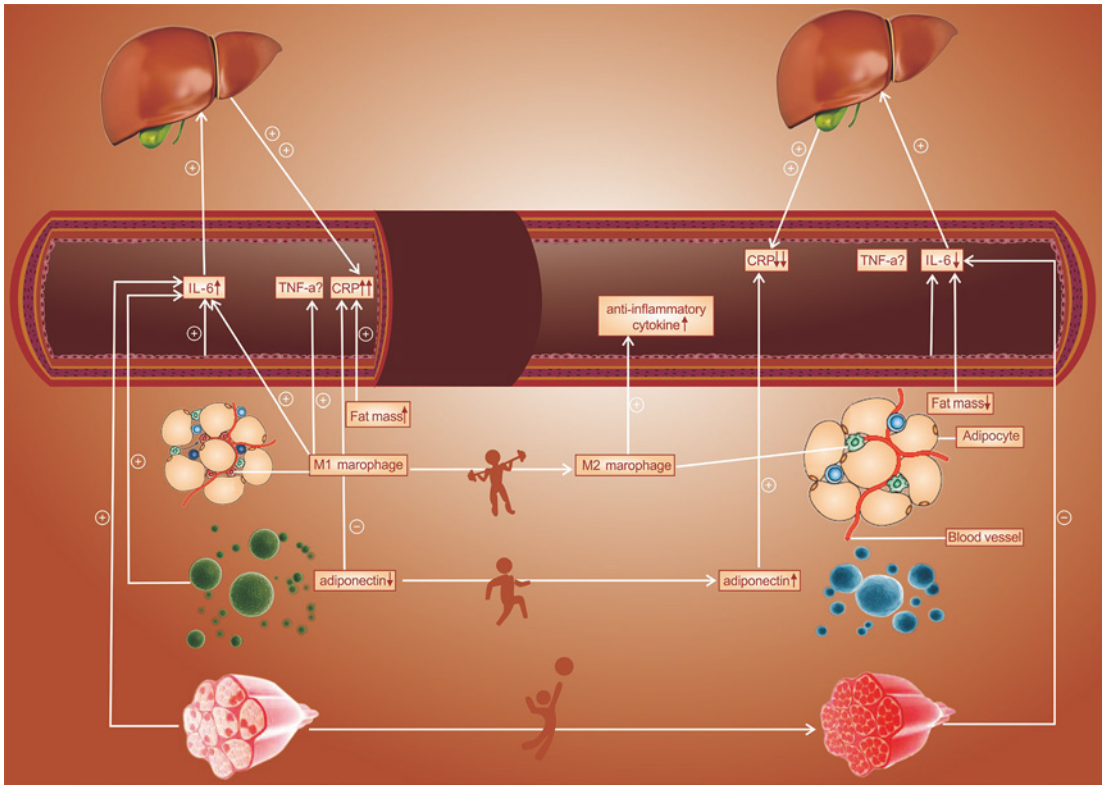

Fig. 5. Potential mechanisms contributing to the anti-inflammatory effects of exercise.

TNF-α, while anti-inflammatory cytokines are produced by M2-type macrophages. It is possible that the phenotypic switch from the M1 macrophage to the M2 macrophage is induced by exercise. Additionally, exercise also prevents M1 macrophage infiltration into adipose tissue [55]. Fourth, physical exercise reduces inflammatory cytokines by improving endothelial function. Through regular exercise, obese youth can decrease their systolic blood pressure, and this was verified in our meta-analysis. Endothelial cells are widely known to secrete IL-1 and IL-6; the generation of IL can be increased through activated endothelia and inflammation can then be induced. Therefore, peripheral inflammatory markers associated with endothelial dysfunction are reduced by regular PA [21], as are soluble vascular cell adhesion molecule-1 (sVCAM-1) and macrophage chemoattractant protein 1 (MCP-1) [23]. Finally, exercise may also regulate inflammatory cytokines, particularly IL-6, via muscle contraction. For IL-6 secretion into the systemic circulation, skeletal muscle might serve as an endocrine mechanism. On the one hand, during and after exercise of a sufficient load, active skeletal muscle markedly increases both cellular and circulating levels of IL-6 [56]. On the other hand, a variety of responses in terms of IL-6 levels have been reported; a decrease was observed in some studies [57, 58] and no change was observed in other studies after intervention programs in obese children [59, 60]. Thus, several likely mechanisms among those listed above contribute to the anti-inflammatory effect of exercise (Fig. 5).

Limitations

This meta-analysis has several limitations. First, regarding obesity and overweight, the definitions are inconsistent. Second, a small number of RCT were included, although the stringency of the conclusion criteria already optimized their homogeneity. Furthermore, this meta-analysis

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had heterogeneity, especially for typology of exercises. The dramatic differences in the types of exercise conducted in the interventions may have impacted the CRP levels, Moreover, the meta-analysis was limited to studies in English, so publication bias may have occurred.

Conclusion

Our study indicated that PA was associated with reduced serum CRP levels, whereas associations with IL-6 and TNF-α in overweight or obese children or adolescents were non-significant, although there was a trend toward a reduction in IL-6. This meta-analysis supports the notion that PA can be used as a therapy for children and adolescents to reverse the low-grade inflammatory state of overweight/obesity, thereby restoring anti-inflammatory levels to those observed in normal-weight youths. In addition, subsequent studies must delineate the mechanisms through which the inflammatory process is affected by exercise.

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Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflict of interests to declare.

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