Exercise and Vascular Function in Child Obesity: A Meta-Analysis

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abstract

CONTEXT: Conduit artery flow-mediated dilation (FMD) is a noninvasive index of preclinical atherosclerosis in humans. Exercise interventions can improve FMD in both healthy and clinical populations.

OBJECTIVE: This systematic review and meta-analysis aimed to summarize the effect of exercise training on FMD in overweight and obese children and adolescents as well as investigate the role of cardiorespiratory fitness (peak oxygen consumption [VO2peak]) on effects observed.

DATA SOURCES: PubMed, Medline, Embase, and Cinahl databases were searched from the earliest available date to February 2015.

STUDY SELECTION: Studies of children and/or adolescents who were overweight or obese were included.

DATA EXTRACTION: Standardized data extraction forms were used for patient and intervention characteristics, control/comparator groups, and key outcomes. Procedural quality of the studies was assessed using a modified version of the Physiotherapy Evidence Base Database scale.

RESULTS: A meta-analysis involving 219 participants compared the mean difference of pre-versus postintervention vascular function (FMD) and VO2peak between an exercise training intervention and a control condition. There was a significantly greater improvement in FMD (mean difference 1.54%, \( P < .05 \)) and VO2peak (mean difference 3.64 mL/kg/min, \( P < .05 \)) after exercise training compared with controls.

LIMITATIONS: Given the diversity of exercise prescriptions, participant characteristics, and FMD measurement protocols, varying FMD effect size was noted between trials.

CONCLUSIONS: Exercise training improves vascular function in overweight and obese children, as indicated by enhanced FMD. Further research is required to establish the optimum exercise program for maintenance of healthy vascular function in this at-risk pediatric population.
Obesity has placed a large burden on the pediatric population over the last 30 years, with steady increases noted in several countries. Pediatric obesity is often carried into adulthood and is associated with risk factors for chronic diseases such as cardiovascular disease and type 2 diabetes. Impaired vascular function may contribute to increased cardiovascular disease risk, as atherosclerosis begins in childhood and endothelial dysfunction has been identified as an early event contributing to the development of atherosclerosis. There is strong evidence that obese children and adolescents have lower arterial compliance and distensibility than their healthy matched controls, as well as depressed (2%) endothelium-dependent and -independent conduit artery vasodilator function.

Endothelial dysfunction is prognostically significant, as it can predict future cardiovascular events, even after established risk factors for atherosclerosis are accounted for. A meta-analysis found that a 1% decrease in flow-mediated dilation (FMD) was associated with a 13% increase in risk of future cardiovascular events. Retarding atherosclerosis with early preventive measures that enhance vascular function may reduce the likelihood of future cardiovascular disease through a reduction of global cardiovascular risk.

Previous reviews in adults found that impaired vasodilator function is improved with exercise training; however, findings are not as consistent in healthy populations with normal vascular function as they are in those with risk factors and cardiovascular disease, in part owing to countervailing changes in vascular function and structure. The aim of this systematic review was to meta-analyze and examine the effects of exercise training on vascular function in obese children and adolescents. Changes in body composition and cardiorespiratory fitness were also evaluated to examine the general efficacy of the exercise intervention and the relationship between cardiorespiratory fitness, body composition, and vascular function improvements.

**METHODS**

We conducted and reported this systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

**Literature Search**

PubMed, Medline, Embase, and Cinahl databases were searched from the earliest available date to February 2015, limited to studies in humans and the English language. The Medical Subject Heading (MeSH) database was used to retrieve all articles related to exercise training and FMD in overweight or obese children and adolescents. MeSH terms used were "obesity" OR "overweight" OR "child" OR "adolescent" OR "atherosclerosis" and their related terms. Text words used in conjunction with the MeSH terms were ("exercise training" OR "physical training" OR "exercise" OR "exercise intervention") AND ("arterial function" OR "vascular function" OR "vascular dysfunction" OR "flow-mediated dilation" OR "endothelium-dependent dilation"). Reference lists of retrieved articles were also searched for other relevant studies.

**Study Inclusion Criteria**

Studies were considered eligible for inclusion if they met criteria regarding population, intervention, comparator, outcomes, and study design. Participants were required to be obese or overweight children or adolescents (according to age- and gender-specific criteria) who completed an exercise intervention using aerobic exercise training of ≥6 weeks in the form of a randomized controlled trial (individual or cluster).

Studies that included exercises additional to aerobic exercise training, such as resistance training or agility training, were also considered. A nonexercise comparator or control group was required for study inclusion. The measurement of FMD was necessary.

We excluded editorials, opinions, studies not published in a peer-reviewed journal, and studies available only as meeting abstracts.

**Study Selection Process**

All abstracts retrieved were screened, and clearly irrelevant studies were excluded. Full texts of all potentially eligible studies were examined. Supplemental Table 3 includes studies that were excluded after full-text examination. Figure 1 outlines the study selection process from initial search to inclusion.

**Data Extraction**

Data were extracted by using a standardized data extraction form. Patient characteristics (age, gender, and overweight/obesity classification), intervention (exercise mode, frequency, duration, intensity, and supervision), control/comparator groups, methodological quality, and key outcomes were noted. Corresponding authors were contacted for information not available in the journal article.

**Risk of Bias Assessment**

Methodological quality of all studies was assessed by 2 independent reviewers using a modified Physiotherapy Evidence Base Database (PEDro) 10-point scale. One point was awarded for each criterion met (Fig 2). The average score was recorded when a discrepancy was noted.

**Data Analysis and Synthesis**

Data synthesis was descriptive, with detailed tabular summaries presented (Tables 1 and 2). For the primary outcome of FMD, data were extracted from all 6 studies, allowing...
a quantitative summary using meta-analysis. For the secondary outcomes of weight/BMI and VO₂peak, data were extracted from 6 and 3 studies, respectively. We compared absolute changes and calculated a weighted mean difference (95% confidence interval [CI]) for each study.

Heterogeneity was investigated by reviewing study populations, methods, and interventions and by using the χ² test for homogeneity and the I² statistic. A fixed-effects model for the meta-analysis was used unless statistical heterogeneity was identified (χ² test $P \leq .05$ or $I^2 \geq 50\%$), for which a random effects model was used. We were unable to undertake a funnel plot for assessment of publication bias given the small number of studies meeting the criteria for meta-analysis. Analyses were conducted by using Review Manager 5.0 (Nordic Cochrane Centre, Copenhagen, Denmark).

RESULTS

Identification and Selection of Studies

The bibliographic search yielded 176 articles (Fig 1). After examining the titles and abstracts, 14 full-text articles were retrieved, with 6 identified as meeting the inclusion criteria.11,12,22–25 The corresponding authors of 4 of these 6 studies were successfully contacted for further data.11,22–24

Risk of Bias

A mean modified PEDro scale score of 8.2/10 was recorded for the 6 studies. All 6 studies satisfied the following criteria: eligibility criteria were specified, participants were randomly allocated to groups, assessors measuring the primary outcome were blinded, results of between-group statistical comparisons were reported for primary outcomes, and both point measures and measures of variability for ≥1 key outcome were provided. PEDro defines a key outcome as the primary measure of therapeutic effectiveness. Only 1 study reported having concealed allocation.12

Study Characteristics

Table 1 summarizes the 6 included trials, which involved 219 participants (116 females and 103
<table>
<thead>
<tr>
<th>Reference</th>
<th>Country</th>
<th>n</th>
<th>Age, years [mean (SD) or range]</th>
<th>Males, %</th>
<th>Overweight/Obesity Definition</th>
<th>Intervention</th>
<th>Intervention Supervision</th>
<th>Control or Comparison</th>
<th>Intervention Duration, wks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farpour-Lambert et al 2009</td>
<td>Switzerland</td>
<td>44</td>
<td>Intervention 9.1 (1.4); control 8.8 (1.6)</td>
<td>36</td>
<td>BMI &gt;97th age- and gender-specific percentile&lt;sup&gt;20&lt;/sup&gt;</td>
<td>CT: 3 1-h sessions/wk; 30 min AEX (walking, running, ball games, swimming) at 55%–65% &lt;br&gt; VO₂max; 20-min RT; 10-min stretching; cool-down</td>
<td>Physical education teachers</td>
<td>No treatment; instructed to maintain current levels of physical activity</td>
<td></td>
</tr>
<tr>
<td>Kelly et al 2004</td>
<td>United States</td>
<td>20</td>
<td>Intervention 11.0 (0.20); control 11.0 (0.22)</td>
<td>45</td>
<td>BMI &gt;85th age- and gender-specific percentile</td>
<td>AEX: 4 sessions/wk; 30-min cycle ergometer at 50%–60% VO₂peak including 5-min warm-up and cool-down; intensity/duration increase each week to reach 70%–80% VO₂peak for 50 min in weeks 7–8</td>
<td>Researchers</td>
<td>No treatment; instructed to maintain current levels of physical activity</td>
<td>12</td>
</tr>
<tr>
<td>Murphy et al 2009</td>
<td>United States</td>
<td>35</td>
<td>Intervention 7–12; control not reported</td>
<td>51</td>
<td>BMI &gt;85th age- and gender-specific percentile (Must 1991)</td>
<td>DDR 5 d/wk; instructed on time and approximate number of songs required to achieve time; recorded daily DDR use and steps took while playing</td>
<td>None</td>
<td>No treatment</td>
<td>12</td>
</tr>
<tr>
<td>Watts et al 2004</td>
<td>Australia</td>
<td>14</td>
<td>8.9 (1.6)</td>
<td>43</td>
<td>BMI ≥30 kg/m² equivalent&lt;sup&gt;26&lt;/sup&gt;</td>
<td>AEX: 3 1-h sessions/wk; whole-body exercise including warm-up, exercise, and stretching; included dodge-and-tag, jogging, soccer at set HR (140–180 bpm); intensity and duration increased as tolerated</td>
<td>Exercise physiologists&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Crossover protocol (randomly assigned to exercise or nontraining period); asked to desist from activity for 8 wks during nontraining period</td>
<td>8</td>
</tr>
<tr>
<td>Watts et al 2004</td>
<td>Australia</td>
<td>19</td>
<td>14.3 (1.5)</td>
<td>47</td>
<td>BMI ≥30 kg/m² equivalent&lt;sup&gt;26&lt;/sup&gt;</td>
<td>CT: 3 1-h sessions/wk; 5 min warm-up, 5 min stretches, 22.5 min AEX on cycle ergometer (85%–85% HR max), 22.5 min RT (55%–70% pretraining strength max), 5 min cool-down</td>
<td>Exercise physiologists&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Crossover protocol (randomly assigned to exercise or nontraining period); asked to desist from activity for 8 wks during nontraining period</td>
<td>8</td>
</tr>
<tr>
<td>Woo et al 2004</td>
<td>Hong Kong</td>
<td>82</td>
<td>Intervention 10.0 (1.0); control 9.9 (0.9)</td>
<td>66</td>
<td>BMI ≥21 kg/m² according to Centers for Disease Control and Prevention</td>
<td>CT: 2 75-min sessions/week; 10 min warm-up, 30 min RT, 10 min AEX (60%–70% HR max), 10 min agility training, 5 min cool-down and short rest periods; diet education program</td>
<td>Physiotherapists</td>
<td>Diet education program by dietitian (2/wk for 6 wks, then 2/mo); balanced hypocaloric diet prescribed (900–1200 kcal daily)</td>
<td>6</td>
</tr>
</tbody>
</table>

<sup>CT</sup>, circuit training; <sup>AEX</sup>, aerobic exercise training; <sup>RT</sup>, resistance training; <sup>HR</sup>, heart rate.

<sup>a</sup> Correspondence with authors.
TABLE 2 FMD Protocols and Outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>Preparation</th>
<th>Cuff Pressure, mm Hg</th>
<th>Time in Ischemia, min</th>
<th>Postischemia Scanning Protocol</th>
<th>Image Analysis</th>
<th>Vascular Function Outcome</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farpour-Lambert et al 2009 &amp; 2012</td>
<td>Supine rest 30 min</td>
<td>300</td>
<td>4</td>
<td>30 s before, 90 s after cuff release</td>
<td>Not reported</td>
<td>FMD peak, %</td>
<td>−0.59</td>
</tr>
<tr>
<td>Kelly et al 2004 &amp; 2012</td>
<td>Fasted (12 h); supine rest 15 min</td>
<td>200</td>
<td>5</td>
<td>180 s after cuff release</td>
<td>Semiautomated, wall tracking software</td>
<td>FMD peak, %</td>
<td>1.10</td>
</tr>
<tr>
<td>Murphy et al 2009 &amp; 2012</td>
<td>Fasted (12 h); no caffeine or exercise for 24 h</td>
<td>50 above resting SBP</td>
<td>5</td>
<td>60 s after cuff release</td>
<td>Manual offline (trained, blinded observer)</td>
<td>FMD peak, %</td>
<td>5.60</td>
</tr>
<tr>
<td>Watts et al 2004 &amp; 2009</td>
<td>Fasted (4 h); no caffeine or exercise; supine rest 20 min</td>
<td>220</td>
<td>5</td>
<td>180 s after cuff release</td>
<td>Semiautomated, wall tracking software</td>
<td>FMD peak, %</td>
<td>1.55</td>
</tr>
<tr>
<td>Watts et al 2004 &amp; 2009</td>
<td>Fasted (4 h); no caffeine or exercise; supine rest 20 min</td>
<td>220</td>
<td>5</td>
<td>180 s after cuff release</td>
<td>Semiautomated, wall tracking software</td>
<td>FMD peak, %</td>
<td>3.50</td>
</tr>
<tr>
<td>Woo et al 2004 &amp; 2009</td>
<td>Fasted (14 h)</td>
<td>250</td>
<td>4.5</td>
<td>30 s before, 90 s after cuff release</td>
<td>Manual offline (trained, blinded observer)</td>
<td>Resting BA diameter</td>
<td>−0.04</td>
</tr>
</tbody>
</table>

AUC, area under the curve; GTN, glyceryl trinitrate; BA, brachial artery
* P < .01
** Correspondence with authors.
* P < .05

males), with 129 and 118 assigned to the exercise intervention and control groups, respectively.

Three of the 6 reviewed studies examined FMD in obese participants only, whereas the remaining 3 studies included both overweight and obese participants. Overweight and obesity criteria varied, with use of the Cole dataset (2000), the Must dataset (1991), and an East German dataset developed by Kromeyer-Hauschild (2007).

Because of the differing criteria for defining obesity, these participants were not meta-analyzed separately.

The World Health Organization defines adolescents as young people between the ages of 10 and 19 years, so 4 of the included studies involved both children and adolescents, and 1 involved children only. Authors specified whether the population of interest was prepubertal, postpubertal, or mixed. Two of the 6 investigations were conducted by the same research group at the University of Western Australia, albeit in different subjects.

Vascular Assessment Protocols
Vascular assessment protocols varied with regard to cuff pressure, time in ischemia, ultrasound scanning duration, and timing after cuff release. All 6 protocols placed the cuff distal to the region of interest as per guidelines. Inflated cuff pressure ranged from 200 to 300 mm Hg, with 1 study inflating pressure to 50 mm Hg above resting systolic blood pressure. The cuff was inflated for 5, 4.5, 4.25, 4.5, or 4.12 minutes. Timing of artery imaging varied, with 2 studies imaging for 30 seconds before and 90 seconds after cuff release. In Kelly et al and both studies by Watts et al, the artery was imaged continuously for 180 seconds after cuff release, whereas Murphy et al imaged the artery for 60 seconds after cuff release. Image analysis was performed by using automated edge detection and wall tracking software in 2 laboratories. Farpour-Lambert et al did not state FMD analysis techniques; Woo et al and Murphy et al stated that scans were analyzed offline by a trained, blinded observer, indicating that manual caliper-based analysis was used. In reporting reliability of the measure, Murphy et al stated their laboratory coefficient of variation for artery diameter, whereas Woo et al reported established FMD coefficient of variation values, as published by Sorensen et al.

Participant preparation varied between protocols. When participants had fasted, fasting time ranged from 4 to 14 hours. Watts et al and Murphy et al also asked participants to abstain from caffeine and exercise for 4 to 24 hours before testing. Additionally, 4 protocols stated that participants rested for a specified time period before vascular assessment.

Exercise Mode
Circuit training was used by 3 studies that incorporated aerobic exercise...
with other activities. Circuit training consisted of a combination of (1) aerobic exercise (walking, running, ball games, and swimming) with resistance training; (2) aerobic exercise on a cycle ergometer with resistance training; and (3) aerobic exercise (modality not stated) with resistance and agility training. In 3 programs, aerobic exercise alone was performed by using (1) a cycle ergometer; (2) activities including dodge-and-tag, jogging, and soccer; and (3) Dance Dance Revolution (DDR). Studies mostly included a warm-up and/or cool-down period.

**Exercise Intensity**

Aerobic exercise intensities were typically based on baseline maximal/peak testing data using a percentage of either maximal heart rate (MHR), \( V_\text{O2max} \) or \( V_\text{O2peak} \). Watts et al prescribed a set heart rate zone (140 to 180 bpm), whereas Murphy et al did not specify or measure intensity of exercise performed. When prescription involved a percentage of maximal/peak oxygen consumption, similar intensities were prescribed (55% to 65% \( V_\text{O2max} \) vs 50% to 60% \( V_\text{O2peak} \)). When MHR was used to define intensity, heart rate ranges specified were 65% to 85% and 60% to 70% MHR. Kelly et al stated that intensity was increased from 50% to 60% to "near" 70% to 80% \( V_\text{O2peak} \) toward the end of the intervention. Of the 3 trials that included circuit training, only 1 specified the intensity of the resistance training (55% to 70% of pretraining maximum strength).

**Exercise Duration**

Farpoour-Lambert et al prescribed 60 minutes of exercise, whereas Woo et al used 75 minutes. Table 1 outlines the subduration of activities performed in this time. In Kelly et al, duration progressed from 30 to 50 minutes in the last 2 weeks, and Murphy et al increased duration from 10 to 30 minutes in week 5, by 5-minute increments each week.

Circuit training was used to incorporate both aerobic exercise and resistance training. Training time of each modality varied, with ratios of 3:1:21, 1:3:24, and 1:1:23 (aerobic exercise:resistance training).

**Exercise Frequency**

Frequency of training sessions ranged from 2 to 5 days/week, with a median of 3 days/week. Woo et al prescribed 2 training sessions each week, whereas Farpoour-Lambert et al and Watts et al prescribed 3 training sessions each week. Among the 3 interventions using a frequency of 3 weekly sessions, the mean difference in FMD per week varied from −0.72% to 3.50%. This variation is likely due to disparities in prescribed modality, duration, and intensity between the studies. These disparities add difficulty in attributing improvements in FMD to a particular session frequency.

**Exercise Supervision**

Three training programs entailed direct supervision for the duration of the intervention. This was provided by 2 experienced physical education teachers, researchers, exercise physiologists, and a team of physiotherapists. A self-administered home program was used in 1 study for the duration of the intervention, and participants did not receive any direct supervision. The researchers used a single training session to teach participants use of DDR equipment and daily logs. Daily logs recorded DDR use and steps taken while playing, which were confirmed with parental signature.

**Exercise Adherence**

When adherence to supervised training sessions was reported, high attendance (83% to 90%) was noted. Murphy et al administered a home-training program in which adherence remained satisfactory, as 75% of participants completed sessions on 5 days per week, and 15% completed sessions on ≥3 days per week.

**Vascular Function**

Pooling the data from the 6 trials, the mean difference in FMD was 1.54% (95% CI 0.24 to 2.84), significantly favoring exercise (Fig 3). Heterogeneity between the studies was displayed, with \( I^2 = 70\% \) and \( \chi^2 \) test \( P = .004 \), and was accounted for using random effects analysis.

Watts et al found that vascular function (FMD) in obese children and...
adolescents was significantly impaired relative to lean age-matched control participants (6.00% ± 0.69% vs 12.32% ± 3.14%, \( P < .0001 \); 5.3% ± 0.9% vs 8.9% ± 0.8%, \( P < .05 \), respectively). The improvement resulting from exercise training normalized vascular function in obese adolescents, with no significant differences seen compared with lean age-matched control participants (8.8% ± 0.8% vs 8.9% ± 1.5%, \( P = \text{NS} \)).

No significant differences were found in brachial artery baseline diameter after the exercise training intervention.\(^{11,22,23,25}\) Because of the influence of vessel size on FMD response, baseline vessel diameter should remain relatively stable for valid comparisons to be undertaken.\(^{33}\)

### Body Composition

The mean difference in weight from the 6 studies was −0.55 kg (95% CI −1.66 to 0.57), favoring exercise (Fig 4). These data were supported by a mean difference of −0.14 kg/m\(^2\) (95% CI −0.60 to 0.32) in BMI, favoring exercise (Fig 5). The mean differences of body composition variables were nonsignificant. The observations were homogeneous between the studies in both analyses, with \( I^2 = 0\% \), \( \chi^2 \) test \( P = 1.0 \) and \( P = .99 \), respectively, and therefore a fixed-effects analysis was performed.\(^{32}\)

### Cardiorespiratory Fitness

After pooling data from 3 studies that included maximal exercising testing and calculation of \( V_{\text{O2peak}} \),\(^{12,22,25} \) the mean difference in cardiorespiratory fitness was 3.64 mL/kg/min (95% CI 1.57 to 5.70), significantly favoring exercise (Fig 6). Again, observations were homogeneous (\( I^2 = 0\% \), \( \chi^2 \) test \( P = .99 \)).

### DISCUSSION

The main finding from this meta-analysis of 219 overweight and obese children and adolescents was that exercise training instigated an improvement in endothelial function. Although exercise training had little effect on body composition, significant increases in cardiorespiratory fitness were noted. Data pooling from 6 studies showed an increase of 1.54% in FMD, whereas data pooling from 3 studies showed an increase of 3.64 mL/kg/min in cardiorespiratory fitness.

The clinical relevance of the improvement in FMD can be assumed from previous prognostic studies. A meta-analysis of 5547 adults associated a 1% increase in FMD with a 13% decrease in cardiovascular events.\(^{13}\) Therefore, an improvement in FMD of 1.54% in this at-risk pediatric population would be expected to ameliorate their cardiovascular risk profile. Further reduction in risk may be contributed by the 1-MET (metabolic equivalents) improvement in cardiorespiratory fitness found in the analyzed studies. Myers et al\(^{34}\) demonstrated that in adults, every 1-MET increase in exercise capacity was associated with a 12% improvement in survival. Whereas elevated BMI, which remained unchanged over the exercise intervention, results in an increased risk of all-cause morbidity and mortality, increased cardiorespiratory fitness confers a reduction in this risk.\(^{35}\)

Previous studies in adult chronic disease populations have shown that exercise training induces changes in FMD. Moderate-intensity exercise training improved endothelium-dependent function in adults with hypertension,\(^{36}\) obesity,\(^{37}\) diabetes,\(^{38}\) coronary disease,\(^{39,40}\) and heart failure,\(^{41}\) whereas no changes were observed in endothelium-independent function.\(^{32}\)

Mechanistically, it is postulated that repetitive exposure to exercise results in upregulation of the nitric oxide dilator system.\(^{17,43}\) The endothelium is activated during bouts of activity owing to mechanical stimulation secondary to increased blood flow and shear stress.\(^{19,43}\) Improvements in endothelium-dependent function can occur independently of improvements in risk factors such as blood lipids, blood pressure, obesity, and glycemic control.\(^{44,45}\)

Although exercise training has been shown to improve vascular function in both animals and humans, these changes are rapidly lost after the cessation of training.\(^{46}\) In patients with a recent myocardial infarction, 4 weeks of exercise training resulted in significant improvements in endothelium-dependent dilation. However, almost complete reversal of the enhancement in endothelium-dependent dilation was reported in a time-equivalent detraining period.\(^{47}\) Woo et al\(^{24}\) examined this effect in a group of participants who withdrew...
from the exercise training with a comparator group who continued to exercise until the 12-month time point. In those who withdrew, FMD returned toward baseline and was significantly lower than directly after the intervention. Even so, FMD of the exercise withdrawal group did remain superior to the control group at 1 year.

Although FMD is diminished in at-risk populations, compensation of vascular structure may occur in overweight and obese youth. Using pulse wave velocity and pulse wave analysis, Charakida et al48 illustrated that overweight and obese children had reduced arterial stiffness compared with normal-weight children. The authors suggested that conduit artery adaptation may occur to subdue the hemodynamic effects of adiposity.48 Tryggestad et al49 proposed that increased artery compliance observed in obese children may be due to advanced growth and maturation compared with normal-weight children. Regardless, the current evidence suggests that overweight and obesity affects vascular function (FMD) and structure (stiffness) dissimilarly. It is also relevant in this context that studies have reported compensatory interrelated changes in vascular function and structure, with initial functional changes ultimately being superseded by changes in artery size and remodeling.19,20

The present meta-analysis was unable to extrapolate a relationship between cardiorespiratory fitness and FMD, as just 3 of the included studies conducted maximal exercise tests.12,22,25 Furthermore, the discrepancies in exercise prescription (mode, intensity, duration, and frequency) between studies add complexities when attempting to ascertain an optimal prescription. Therefore, the exact exercise prescription required to induce clinically significant improvements in FMD cannot be established until more data become available. It is also important to reinforce the competing effects of exercise on body composition and the consequent difficulty in using body weight indices such as BMI. Several studies have reported that, although body weight and BMI are not decreased by exercise training, beneficial countervailing effects occur through increases in lean body mass and decreases in fat mass.11,23 We recommend that future studies focus on the impact of exercise training on body composition, not BMI or body weight.

Limitations

Although this review does illustrate the positive impact of exercise on FMD, a measure of vascular function, the included studies had methodological limitations. Heterogeneity of the FMD measure was high ($\chi^2 = 17.53, I^2 = 70\%$, $P = .004$), perhaps owing to varying exercise training regimens or technical preparation and analytical approaches. Although this limitation suggests that results should be interpreted with caution owing to variation in true effect sizes, statistical heterogeneity was addressed through random effects modeling within the meta-analysis. The optimum exercise training protocol to maximize health benefits in obese pediatric populations is yet to be established. As such, current research consists of varying exercise modes and intensity as well as differing session duration and frequency. Furthermore, heterogeneity may be due to the different FMD measurement protocols used, with

<table>
<thead>
<tr>
<th>Study</th>
<th>MD (95% CI)</th>
<th>MD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farpour-Lambert et al 200912</td>
<td>-0.20 (-0.71 to 0.31)</td>
<td>-0.14 (-0.60 to 0.32)</td>
</tr>
<tr>
<td>Kelly et al 200422</td>
<td>0.10 (-6.42 to 6.62)</td>
<td></td>
</tr>
<tr>
<td>Murphy et al 200923</td>
<td>-0.40 (-6.14 to 5.34)</td>
<td></td>
</tr>
<tr>
<td>Watts et al 200411</td>
<td>0.00 (-3.60 to 3.60)</td>
<td></td>
</tr>
<tr>
<td>Watts et al 200423</td>
<td>0.30 (-2.38 to 1.78)</td>
<td></td>
</tr>
<tr>
<td>Woo et al 200424</td>
<td>0.30 (-0.99 to 1.59)</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>-0.14 (-0.60 to 0.32)</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 0.54; I^2 = 0\%; P = 0.99$
Test for overall effect $Z = 0.60; P = 0.55$

**FIGURE 5**
Forest plot illustrating treatment effect of exercise on BMI compared with control. MD, mean difference.
evolving guidelines and technology the primary source of this variability. Discrepancies were present in image acquisition alongside analysis techniques, ie, automated software compared with user-dependent manual measurements, which are likely to influence the outcome. A recent guidelines document was produced to overcome some of the technical difficulties between laboratories using the FMD approach. The current review did not include studies of vascular structure, measured as arterial stiffness, because of a limited number of studies reporting both vascular function (FMD) and structure (arterial stiffness) measures. Furthermore, publication bias may have been introduced by limiting the meta-analysis to studies in the English language.

Whereas the mean difference of FMD% was 1.54%, this value lies within the range of variability of the different protocols. It is important to note, however, that 5 of the 6 studies reported improvements greater than the clinically significant value of 1.0%. Furthermore, 3 of these studies used the gold standard automated analysis approach, suggesting greater reliability and validity of findings.

Most studies reviewed involved small sample sizes, with a total of 219 participants included in the meta-analysis, and male-to-female ratios were unequal in 2 of 6 studies. Differing study and participant characteristics such as chronological and maturational age are confounding factors that may have influenced FMD results. Not only did the criteria for overweight and obesity vary between reviewed studies, but 3 of 6 studies presented pooled FMD data for overweight and obese participants, therefore restricting the meta-analysis to the entire population. Combining overweight and obesity may result in varying stages of vascular dysfunction among the population studied. The influence of exercise at each stage of vascular remodeling and dysfunction is currently unknown. Further research concentrating on specific populations with particular exercise interventions will allow for more concise prescription guidelines to become available.

Feasibility

Strong adherence to any exercise program is required for short- and long-term efficacy. In the studies identified in this review, adherence was high, ranging from 83% to 90% in supervised programs. However, long-term adherence to the intervention was not examined, ie, whether individuals continue the exercise program after the supervised exercise-training period. Previous examinations of the effectiveness of lifestyle interventions in pediatric obesity suggest that these interventions are effective in improving cardiometabolic outcomes for ≤1 year. Again, uncertainty surrounds the effectiveness of such programs over a longer period of time.

Practitioners and public health officials face much difficulty in encouraging regular exercise among children and adolescents. Current worldwide data suggest that only 5% to 50% of children and adolescents are meeting physical activity guidelines (60 minutes each day), implying that permanent adoption of daily physical activity and exercise in these populations may be difficult. Supervision and enjoyment are components positively related to adherence, and consideration must be made when designing a training program. Watts et al designed a game-based exercise program involving activities such as dodge-and-tag, jogging, and soccer, which resulted in a high attendance rate. Educating children and adolescents about ways to incorporate regular exercise into daily routines may be helpful in establishing appropriate lifestyle behaviors from an early age. Large, longitudinal studies are required to further investigate this notion. Although the current evidence regarding physical activity tracking throughout life is mixed, several studies suggest that physical activity behaviors in late childhood and early adolescence can track into adulthood, emphasizing the importance of early-life interventions.

CONCLUSIONS

This meta-analysis indicates that exercise is able to induce improvements in FMD in overweight and obese children and adolescents. The magnitude of increase (~1.5%) would be expected to restore diminished vascular function reported in this at-risk pediatric population. This review therefore supports the notion that exercise can be used as a therapy in pediatric obesity to reverse reduced vascular function, restoring FMD to levels comparable to those observed in normal-weight children and adolescents. Considering the heterogeneity and small sample size of this analysis, further research is warranted to establish dose-response effects together with optimal exercise modality. Extended postintervention follow-up will ascertain the long-term sustainability of exercise in the treatment of diminished vascular function.

ABBREVIATIONS

CI: confidence interval
DDR: Dance Dance Revolution
FMD: flow-mediated dilation
MeSH: Medical Subject Heading
MHR: maximal heart rate
PEDro: Physiotherapy Evidence Base Database
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Exercise and Vascular Function in Child Obesity: A Meta-Analysis
Katrin A. Dias, Daniel J. Green, Charlotte B. Ingul, Toby G. Pavey and Jeff S. Coombes
Pediatrics 2015;136:e648
DOI: 10.1542/peds.2015-0616 originally published online August 10, 2015;

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