Exercise and Insulin Resistance in Youth: A Meta-Analysis

BACKGROUND AND OBJECTIVES: The prevalence of obesity and diabetes is increasing among children, adolescents, and adults. Although estimates of the efficacy of exercise training on fasting insulin and insulin resistance have been provided, for adults similar estimates have not been provided for youth. This systematic review and meta-analysis provides a quantitative estimate of the effectiveness of exercise training on fasting insulin and insulin resistance in children and adolescents.

METHODS: Potential sources were limited to peer-reviewed articles published before June 25, 2013, and gathered from the PubMed, SPORTDiscus, Physical Education Index, and Web of Science online databases. Analysis was limited to randomized controlled trials by using combinations of the terms adolescent, child, pediatric, youth, exercise training, physical activity, diabetes, insulin, randomized trial, and randomized controlled trial. The authors assessed 546 sources, of which 4.4% (24 studies) were eligible for inclusion. Thirty-two effects were used to estimate the effect of exercise training on fasting insulin, with 15 effects measuring the effect on insulin resistance. Estimated effects were independently calculated by multiple authors, and conflicts were resolved before calculating the overall effect.

RESULTS: Based on the cumulative results from these studies, a small to moderate effect was found for exercise training on fasting insulin and improving insulin resistance in youth (Hedges’ d effect size = 0.48 [95% confidence interval: 0.22–0.74], P < .001 and 0.31 [95% confidence interval: 0.06–0.56], P < .05, respectively).

CONCLUSIONS: These results support the use of exercise training in the prevention and treatment of type 2 diabetes. Pediatrics 2014;133:e163–e174
The global prevalence of pediatric type 2 diabetes mellitus (T2DM) has paralleled the rise in obesity, increasing steadily since the late 1970s. This endocrine disorder is caused by a combination of peripheral insulin resistance (IR) in muscle and adipose tissue and inadequate insulin secretion from the pancreas, eventually resulting in a relative insulin deficiency. Early dysfunction in β-cell activity and cellular IR appear long before manifestation of the signs and symptoms of T2DM. Puberty is marked by a decrease in physical activity and an increase in adiposity, and both are associated with IR in youth. In the clinical setting, physical activity and dietary intervention are recommended as the primary treatment methods for pediatric patients in the early stages of IR and prediabetes, with pharmacologic treatment reserved as an alternative course of action as the disease progresses.

The American College of Sports Medicine presents a strong body of evidence supporting the inclusion of physical activity and exercise in the treatment and management of diabetes in adults and youth. Together, physical activity and lifestyle modifications can effectively reduce the development of and/or slow the progression of IR. Previous reviews have established that aerobic and resistance training can be used to improve the regulation of glucose, as well as provide a synergistic effect when combined in a structured exercise program across all ages. Although previous original research and subsequent reviews provide the basis for including physical activity and exercise training in the treatment program for the prevention of T2DM, meta-analytic reviews of exercise and fasting insulin have been limited to adults or children and adolescents with type 1 diabetes. The current study expands on the body of literature by providing a quantitative estimate of the effect size (ES) of exercise training on fasting insulin and IR for use in future research and program design with children and adolescents.

**METHODS**

The review was conducted in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement guidelines. Articles published by June 25, 2013, were located by using searches of the PubMed, SPORTDiscus, Physical Education Index, and Web of Science online databases using combinations of the terms adolescent, child, pediatric, youth, exercise training, physical activity, diabetes, insulin, randomized trial, and randomized controlled trial. Duplicate publications were removed. The authors manually reviewed reference lists from retrieved articles for additional publications not discovered by using the database search.

**Study Selection**

The inclusion criteria for our analysis were as follows: (1) peer-reviewed publication; (2) available in English; (3) involving human subjects; (4) randomized to exercise training or a nonexercise comparison; and (5) fasting insulin or IR measures at baseline, during, and/or after exercise training. Excluded records had the following characteristics: (1) were non–peer reviewed; (2) provided a review, meta-analysis, position statement, or proposed study design; (3) sampled subjects aged <6 or >19 years; (4) used a cross-sectional or prospective study design; (5) included exercise as 1 part of a multicomponent treatment (eg, exercise + diet), from which an ES for exercise alone could not be calculated; or (6) compared exercise only with an active treatment (eg, nutritional intervention or another mode of exercise). A total of 546 articles were identified during the initial search process. A flowchart of study selection is provided in Fig 1. Manual searches revealed 5 additional publications. Six articles reported fasting insulin measurements as median and interquartile range (25th–75th percentile), reported data in change scores from baseline, or did not report either premeasurement or postmeasurement data. A request for missing data was sent to each of the corresponding authors. Two of the 6 authors provided missing information and 1 author provided an additional publication not obtained during our initial literature search; these 3 articles were included in the final meta-analysis.

**ES Calculation**

ES values were calculated by subtracting the mean change in the comparison condition from the mean change in the exercise condition and dividing the difference by the pooled SD of the baseline scores. SDs from the largest study available were used to estimate the ES when group mean values and measures of variability were not provided. Postintervention values in these publications were reported as change scores or in figures provided by the authors. ES values were calculated after adjusting for small sample bias. IR was calculated by using fasting levels of insulin and glucose by using the homeostasis model assessment (HOMA) technique in each study included in this analysis. A decrease in fasting insulin levels or IR among participants in exercise interventions resulted in a positive ES. Two authors (M.V.F. and N.H.G.) independently calculated ES from each study, and discrepancies were resolved before aggregating effects.

**Statistical Analysis**

Random effects models were used to aggregate a mean ES and 95% confidence interval (CI) for fasting insulin and IR to test variation in effects.
according to moderator variables by using macros (MeanES and MetaReg) in IBM SPSS version 20.0 (IBM SPSS Statistics, IBM Corporation, Armonk, NY). The number of potential moderators was restricted due to the small number of effects. Univariate linear regression was then used to estimate the independent effect of exercise on fasting insulin level based on baseline pubertal status, gender, and BMI, chosen a priori due to their strong influence on fasting insulin and metabolic syndrome in this population.7,42 Because effects were nested within studies, a multilevel mixed model linear regression model with robust maximum likelihood estimation was also used to adjust for between-study variance and correlated effects within studies according to standard procedures43,44 by using Mplus 7.0.45 Parameters and their errors were estimated with clustering on study by using the Huber-White sandwich estimator to calculate SEs that are robust to heteroscedasticity and correlated effects.46-48 The effect of each moderator on fasting insulin effects was tested separately by comparing each conditional model (which included the intercept and the moderator) with the unconditional intercept-only model by using a likelihood ratio test and the adjusted Bayesian information criterion (BIC).45 Significant interactions were decomposed by using 95% CIs.44,49

RESULTS

Thirty-two effects were derived from 24 studies, with 1599 children measured at

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**FIGURE 1** Flowchart of study selection.
baseline. Data available for study and participant characteristics are presented as mean ± SD. Sample size ranged from 8 to 140 subjects per treatment group (25.4 ± 23.8 subjects per group). Each of the exercise training interventions varied in design and included aerobic, resistance, and a combination of training modes. Study intervention length, frequency, duration, and intensity were reported inconsistently across effects. Exercise training consisted of 3.2 ± 1.0 sessions per week, 55.4 ± 20.0 minutes at a moderate to vigorous intensity physical activity per session for 15.5 ± 11.4 weeks, when reported. The descriptive characteristics of studies included in the analysis are provided in Table 1.

Participant characteristics for each exercise treatment condition were inconsistently reported as well. When reported, the exercise treatment conditions were 54.3 ± 30.8% female and 11.4 ± 28.0% age of age. The ages of participants ranged from 6 to 19 years, with 30 of the 32 effects involving children and adolescents with a mean age >9 years. Effects were derived from treatment groups of normal weight, overweight, and obese participants, with a mean BMI of 27.2 ± 4.9. Mean weight and relative adiposity (ie, percentage of body fat) were 64.5 ± 19.8 kg and 34.9 ± 7.5%, respectively.

The cumulative results of 32 effects gathered from 24 studies published between 1999 and 2013 agree that exercise training effectively reduces IR with a mean ES of 0.31 (95% CI: 0.06–0.56), z = 2.39, P < .05 (Figure 3). In the multilevel, intercept-only model \( \chi^2 = 2(2) = 49.4, \text{BIC} = 48.7 \), the mean ES for IR was 0.32 (95% CI: 0.06–0.58) with marginally significant variance (0.116, \( \text{SE} = 0.068, z = 1.69, P = .09 \)) between effects. Twelve (80.0%) of the 15 effects were larger than zero. These results were consistent for male and female subjects, regardless of age or ethnicity. Forest plots for the effect of exercise training on fasting insulin and IR are shown in Figs 2 and 3, respectively.

Moderator analysis further adjusted for nesting of effects within a single study and to reduce the likelihood of potential bias being introduced into the analysis. Sixteen of the 32 effects for fasting insulin were gathered from studies that provided multiple effects. Two effects could be calculated when information was reported for multiple demographic groups,42 disease populations,31 training intensities,33 or training durations,33 or training modes within a single study.26,40,50,51 Six of the 15 effects examining IR were gathered studies providing multiple effects.31,32,40

Rater Agreement

Two-way (effects × raters) intraclass correlation coefficients for absolute agreement were calculated to examine intrarater reliability for fasting insulin and IR ES. The initial intraclass correlation coefficients for fasting insulin, based on 32 effects, were ≥0.99. After performing the intraclass correlation analysis for the 15 effects measuring the effect of exercise on IR, the coefficients were ≥0.93. Intraclass correlation increased to 100% after adjusting for discrepancies between reviewers (M. V.F. and N.H.G.).

Homogeneity of Results

Heterogeneity was indicated if \( Q_{\text{total}} \) reached a significance level of \( P < .05 \) and the sampling error accounted for <75% of the observed variance.29 Heterogeneity was also assessed by examination of the \( I^2 \) statistic.52 An \( I^2 \) value was categorized as low, moderate, or high based on calculations equal to 25%, 50%, or 75%, respectively. The significant improvement in fasting insulin levels after exercise training was highly heterogeneous (\( Q_{9} = 162.9, P < .001, I^2 = 81.6\% \)), with sampling error accounting for 24.4% of the observed variance. The significant improvement in IR after exercise training was moderately heterogeneous (\( Q_{4} = 30.67, P < .01, I^2 = 57.6\% \)), with sampling error accounting for 48.5% of the observed variance. Based on a significant \( Q \) statistic and an \( I^2 ≥50\% \) indicating moderate heterogeneity, the variability among fasting insulin is greater than would have occurred naturally based on study sample error. The null hypothesis for homogeneous distribution was rejected, and regression analysis was thus used to identify potential moderators.

Pubertal status was determined according to reported Tanner stage. Eleven studies did not provide pubertal status in a usable form for our analysis because: (1) it was not reported at all;23,24,26,27,38,40,53; (2) it was reported in a range of stages34, or (3) it was reported for the entire sample.22,32 The initial regression model based on baseline BMI (\( \kappa = 28 \)) was significant (\( R^2 = 0.15, \beta = 0.38, z = 2.25, P < .05 \)). Gender (\( \kappa = 27 \)) and pubertal status (\( \kappa = 16 \)) were not independently associated with the effect of exercise on fasting insulin in the age range of our analysis (\( R^2 = 0.07, \beta = 0.26, z = 1.44 \) and \( R^2 = 0.08, \beta = –0.28, z = –1.18, \) respectively; all \( P > .05 \)). BMI remained significant after controlling for gender in a multivariate regression analysis based on 26 effects reporting both moderating variables (\( \beta = 0.44, z = 2.61, P < .01 \)). Because the number of effects included in the regression analysis decreased to 13 when gender, pubertal status, and BMI
TABLE 1 Studies Examining the Effect of Exercise Training on Fasting Insulin and IR in Children and Adolescents

<table>
<thead>
<tr>
<th>Source</th>
<th>N</th>
<th>Gender (M/F)</th>
<th>Age (y)</th>
<th>Intervention Groups</th>
<th>Duration (min/d)</th>
<th>Frequency (d/wk)</th>
<th>Study Length (wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benson et al.35 2008</td>
<td>78</td>
<td>46/32</td>
<td>12.3 ± 1.3</td>
<td>RT or CON</td>
<td>—</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Ben Ounis et al.34 2008</td>
<td>24</td>
<td>24/0</td>
<td>12–14</td>
<td>AT, AT + diet, or diet</td>
<td>—</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Buchan et al.31 2011</td>
<td>57</td>
<td>10/47</td>
<td>16.4 ± 0.7</td>
<td>Moderate-intensity AT, high-intensity AT, or CON</td>
<td>3–20</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Davis et al.33 2012</td>
<td>222</td>
<td>94/128</td>
<td>9.4 ± 1.1</td>
<td>High-dose AT, low-dose AT, or CON</td>
<td>20–40</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>Davis et al.36 2009</td>
<td>41</td>
<td>0/41</td>
<td>15.2 ± 1.1</td>
<td>RT + diet, RT + AT + diet, or CON</td>
<td>60</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>Davis et al.29 2009</td>
<td>54</td>
<td>28/26</td>
<td>15.5 ± 1.0</td>
<td>RT + diet, diet, or CON</td>
<td>60</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>Davis et al.36 2011</td>
<td>38</td>
<td>0/38</td>
<td>15.8 ± 1.1</td>
<td>RT + diet, RT + AT + diet, diet, or CON</td>
<td>60–90</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>de Piano et al.37 2012</td>
<td>58</td>
<td>27/31</td>
<td>16.5 ± 1.4</td>
<td>RT + diet, RT + AT + diet, or diet</td>
<td>60</td>
<td>3</td>
<td>52</td>
</tr>
<tr>
<td>Farpour-Lambert et al.51 2009</td>
<td>44</td>
<td>16/28</td>
<td>8.9 ± 1.5</td>
<td>RT + AT or CON</td>
<td>60</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Ferguson et al.52 1999</td>
<td>79</td>
<td>26/53</td>
<td>9.5 ± 1.0</td>
<td>AT or CON</td>
<td>40</td>
<td>5</td>
<td>16</td>
</tr>
<tr>
<td>Gutfun et al.38 2011</td>
<td>242</td>
<td>0/242</td>
<td>8–11</td>
<td>RT + AT + games or CON</td>
<td>80</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Hassan et al.33 2012</td>
<td>100</td>
<td>39/61</td>
<td>15.4 ± 1.1</td>
<td>RT + diet or diet</td>
<td>—</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>Karacabey,53 2009</td>
<td>40</td>
<td>40/0</td>
<td>11.8 ± 0.5</td>
<td>AT or CON</td>
<td>30–60</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Kelly et al.39 2004</td>
<td>20</td>
<td>9/11</td>
<td>10.8 ± 2.0</td>
<td>AT or CON</td>
<td>30–50</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Kim et al.39 2006</td>
<td>26</td>
<td>26/0</td>
<td>17.0 ± 0.1</td>
<td>AT or CON</td>
<td>40</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Kim et al.37 2008</td>
<td>17</td>
<td>17/0</td>
<td>11.0 ± 0.0</td>
<td>RT + AT or CON</td>
<td>50</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>Lau et al.50 2004</td>
<td>36</td>
<td>24/12</td>
<td>10–17</td>
<td>AT or diet + diet</td>
<td>60</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Lee et al.51 2012</td>
<td>45</td>
<td>45/0</td>
<td>12–18</td>
<td>RT, AT, or CON</td>
<td>60</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>McCormack et al.51 2013</td>
<td>18</td>
<td>5/13</td>
<td>13.0 ± 1.9</td>
<td>RT + AT or CON</td>
<td>60</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Meyer et al.55 2006</td>
<td>67</td>
<td>34/33</td>
<td>14.7 ± 2.2</td>
<td>AT or CON</td>
<td>60–90</td>
<td>3</td>
<td>24</td>
</tr>
<tr>
<td>Shaibi et al.56 2006</td>
<td>21</td>
<td>21/0</td>
<td>15.4 ± 1.6</td>
<td>RT or CON</td>
<td>60</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>Shalitin et al.57 2009</td>
<td>162</td>
<td>81/81</td>
<td>6–11</td>
<td>RT + AT, RT + AT + diet, or diet</td>
<td>90</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Suh et al.58 2011</td>
<td>30</td>
<td>15/15</td>
<td>13.1 ± 0.5</td>
<td>RT + diet, AT + diet, or diet</td>
<td>40–60</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Sun et al.59 2011</td>
<td>93</td>
<td>48/47</td>
<td>13.6 ± 0.7</td>
<td>AT, diet, AT + diet, or CON</td>
<td>40</td>
<td>4</td>
<td>10</td>
</tr>
</tbody>
</table>

Age is reported as mean ± SD when available or the age range of participants included in the study. Empty cells are present when a component of the training protocol was not provided by the author. AT, aerobic training; CON, control group; F, female; M, male; RT, resistance training.

were included together in the model, a thorough multivariate analysis including all 3 moderators was not performed. In the multilevel model, adding BMI (β = 0.05, SE = 0.026, z = 1.97, P = .049) improved model fit (χ² [3] = 119.6, BIC = 120.28) compared with the intercept-only model (χ² [1] = −10.8, P < .001). The residual variance was 0.301 (SE = 0.177, z = 1.70, P = .089), indicating that 44% of the variance between fasting insulin effects was explained by BMI.

The regression analysis was repeated to examine the potential moderating influence of gender, pubertal status, and BMI on IR. Based on the univariate analysis of each potential moderator, the regression models were not significant (all P > .05). Gender (β = −0.05, z = −0.17), pubertal status (β = 0.11, z = 0.20), and BMI (β = 0.35, z = 1.50) were not significantly associated with IR. However, adding BMI to the multilevel model for IR (β = 0.03, SE = 0.014, z = 1.78, P = .075) improved model fit (χ² [3] = 40.4, BIC = 39.0) compared with the intercept-only model (χ² [1] = −70.2, P < .001). The residual variance was 0.066 (SE = 0.047, z = 1.40, P = .161), indicating that 43% of the variance between IR effects was explained by BMI after adjusting for nesting of effects within studies.

**Fail Safe-N**

The number of unpublished or unretrieved null effects that would diminish the significance of observed effects to a nonsignificant value exceeds 5N+10, in which N represents the number of original effects. A fail-safe N is a calculation that provides a method to estimate when publication bias can be safely ignored and should not be considered as a method for identifying or controlling for potential effects. From multiple studies of average sample size needed to reach a similar null conclusion. The fail-safe N for the measures of fasting insulin estimated N+= 534.7 and N = 368.1 effects by using the calculations for a fixed effects model suggested by Rosenberg. The estimated random effects model resulted in N1 = 16.5, while N+ collapsed to a fixed effects model. The fail-safe N for the effect of exercise on IR estimated with the fixed effects model was N1 = 22.9 and N+ = 27.2. Based on earlier research from Rosenthal, the fail-safe N is considered robust when the value exceeds 5N+10, in which N represents the number of original effects. A fail-safe N is a calculation that provides a method to estimate when publication bias can be “safely ignored” and should not be considered as a method for identifying or controlling for potential
publication bias.\textsuperscript{54} Potential publication bias was addressed by using a funnel plot and the Egger test.\textsuperscript{56} Funnel plots provide a visual assessment of possible publication bias and identify potential outliers. Funnel plots for the effect of exercise training on fasting insulin and IR can be found in Figs 4 and 5, respectively. The Egger test was used to assess whether the variation in ES was due to potential publication bias. Our results suggest the mean effect of exercise training on fasting insulin and IR was not subject to publication bias ($F_{1,30} = 0.003$ [$P = .95$] and $F_{1,13} = 0.05$ [$P = .83$], respectively).

### Effect of Potential Outliers

Nine effects from the 8 studies outside of the 95% CI were identified by using the forest plot to identify potential outliers.\textsuperscript{23,25,28,40,51,53,57,58} Sensitivity analysis removing these 9 effects decreased the mean effect of exercise on fasting insulin in children and adolescents from

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**FIGURE 2**
Forest plot of Hedges’ d ES. The aggregated Hedges’ d is the random effects mean ES for exercise training on fasting insulin weighted by the pooled SD.
Posttreatment Assessment

<table>
<thead>
<tr>
<th>Study</th>
<th>Hedges’ d (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sun et al. 2011</td>
<td>–0.54 (–1.17 to 0.08)</td>
</tr>
<tr>
<td>Sun et al. 2011</td>
<td>–0.43 (–0.99 to 0.13)</td>
</tr>
<tr>
<td>Farough-Lambert et al. 2009</td>
<td>–0.19 (–0.78 to 0.40)</td>
</tr>
<tr>
<td>Davis et al. 2009</td>
<td>0.11 (–0.53 to 0.75)</td>
</tr>
<tr>
<td>Davis et al. 2011</td>
<td>0.22 (–0.87 to 1.31)</td>
</tr>
<tr>
<td>de Piano et al. 2012</td>
<td>0.22 (–0.52 to 0.96)</td>
</tr>
<tr>
<td>Benson et al. 2008</td>
<td>0.27 (–0.21 to 0.76)</td>
</tr>
<tr>
<td>Shalitin et al. 2009</td>
<td>0.31 (–0.13 to 0.75)</td>
</tr>
<tr>
<td>Kim et al. 2007</td>
<td>0.32 (–0.46 to 1.10)</td>
</tr>
<tr>
<td>McCormack et al. 2013</td>
<td>0.35 (–0.59 to 1.29)</td>
</tr>
<tr>
<td>de Piano et al. 2012</td>
<td>0.67 (–0.07 to 1.40)</td>
</tr>
<tr>
<td>Meyer et al. 2006</td>
<td>0.75 (0.25 to 1.24)</td>
</tr>
<tr>
<td>Hasson et al. 2012</td>
<td>0.78 (0.11 to 1.46)</td>
</tr>
<tr>
<td>Hasson et al. 2012</td>
<td>1.17 (0.43 to 1.91)</td>
</tr>
<tr>
<td>Ben Dunis et al. 2008</td>
<td>1.21 (0.15 to 2.28)</td>
</tr>
</tbody>
</table>

FIGURE 3
Forest plot of Hedges’ d ES. The aggregated Hedges’ d is the random effects mean ES for exercise training on IR weighted by the pooled SD.

0.48 (95% CI: 0.22–0.74; z = 3.57; P < .001) to 0.34 (95% CI: 0.19–0.48; z = 4.51; P < .001) for the remaining 24 effects. When examining IR, 3 effects from 2 studies outside of the 95% CI were identified by using the forest plot to identify potential outliers.40,57 Removing these 3 effects increased the mean effect of exercise on fasting insulin in children and adolescents from 0.31 (95% CI: 0.04–0.57; z = 2.39; P < .05) to 0.38 (95% CI: 0.19–0.57; z = 3.97; P < .001) for the remaining 12 effects.

DISCUSSION

The cumulative results of our analysis support the belief that exercise is effective in decreasing fasting insulin and improving IR in children and adolescents. Our results are unique in that they provide a quantitative estimate of the effect of exercise on outcome measures of insulin, while assessing the influence of potential moderators, including BMI and sexual maturation. Although performed in a separate clinical population, our results are consistent with a previous meta-analysis that evaluated the effect of exercise on glycemic control in children and adolescents with type 1 diabetes (ES = 0.37 [95% CI: 0.02–0.77]).20 Regular physical activity and exercise training should be included as an effective component of a treatment program for T2DM in children and adolescents.

Exercise seems to be most effective in improving insulin status in children and adolescents with high BMI, most likely because these individuals exhibit the greatest deviation from normal values. Physical activity interventions designed to improve cardiometabolic risk may have a small effect in children unless they are selected specifically for their unfavorable risk profiles.28 Obese adolescents showed significantly greater IR than their lean peers, which may provide a “floor effect” and greater room for improvement after training in overweight and obese adolescents.38 As hypothesized, BMI was found to moderate the effect of exercise on fasting insulin in our study sample such that a greater effect was observed in children and adolescents with higher BMI. Translating these research findings into a measurable improvement in clinical outcomes would equate to a 11.4-U/mL (95% CI: 5.2–17.5) improvement in fasting insulin and an improvement in HOMA-IR of 2.0 (95% CI: 0.4–3.6) in obese children, based on recent estimates from Körner et al.59

Based on the results of the regression analysis, the effect of exercise training on fasting insulin was not affected by pubertal status of the child. Puberty is marked by significant changes in fasting insulin and IR. The transient physiologic IR experienced at the beginning of puberty (Tanner stage 2) typically peaks during Tanner stage 3 and returns to prepubertal levels during Tanner stage 5.7,60 Over a 2-year period, children who remained at Tanner stage 1 experienced a small increase in insulin-like growth factor 1, whereas children who matured from stage 1 to stage 3 or 4...
experienced a 1.7-fold increase in insulin-like growth factor 1, accompanied by a 39% decrease in insulin sensitivity. It is intuitive that exercise training may be the most effective for children and adolescents when IR is greatest; however, our analysis was not sufficiently powered to detect these differences. Further research is needed to fully examine the effect of exercise training on fasting insulin and IR when accounting for other moderators because changes in insulin sensitivity during puberty are attenuated when controlling for changes in body mass. In our regression model, the percentage of male participants in each effect did not significantly influence the effect of exercise on fasting insulin or IR. Female subjects typically exhibit higher fasting insulin, greater IR, and are less insulin sensitive during adolescence; however, the changes are consistent across genders. One-half of the gender-related differences in fasting insulin and IR could be explained by differences in adiposity in a group of 357 white and African-American adolescents. Fasting insulin among 11 adolescent girls was significantly higher than among 13 adolescent boys; however, BMI was again found to be a significant covariate. Further research is needed to examine the moderating effect of gender on fasting insulin and IR after exercise training.

A variety of training interventions were used across studies, including resistance training, aerobic training, and circuit training, as well as nontraditional games and play to increase the physical activity levels of the participants. However, after accounting for the influence of participant BMI, these potential moderators did not affect our outcome. We found no difference between aerobic or resistance training protocols, suggesting the most important component of an exercise program designed to target fasting insulin and IR in children and adolescents may not be “how” they are encouraged to move but simply that they encouraged to move at all. More research is needed to determine the most effective delivery mode for the intervention that will be sustainable and encourage longer term adherence and behavior change in participants. For example, a circuit training approach

FIGURE 4
Funnel plot of Hedges’ d ES versus study SE. The aggregated Hedges’ d is the random effects mean ES for exercise training on fasting insulin weighted by the pooled SD.

FIGURE 4
allowed sedentary overweight and obese adolescents to train at 70% to 85% of their maximum heart rate for 60 to 90 minutes by dividing their exercise training into 2-minute bouts followed by 1 minute of recovery between activities. Davis et al suggest training programs involving a combination of aerobic and resistance training can incorporate short aerobic intervals into circuit training and allow overweight and obese adolescents with low aerobic fitness to accumulate the required duration of aerobic exercise and improve adherence by incorporating smaller, more manageable exercise bouts.

Study duration of the exercise intervention was not a significant moderator of the effect of exercise on fasting insulin secretion, despite a previous hypothesis by other researchers that short and long interventions could influence fasting insulin secretion differently. Improvement in fasting insulin and IR can occur after exercise training in the absence of improvements in weight or body composition. Short-term interventions may improve IR by acting peripherally to improve insulin sensitivity in the muscle, whereas long-term interventions may improve body composition and improve IR through other mechanisms. Because our results suggest the length of the intervention may not significantly influence insulin response to training, further research is needed to thoroughly evaluate this hypothesis in children.

These results provide the basis for including physical activity and exercise training in the treatment program for the prevention of T2DM. However, a void in the literature has been identified, and additional well-designed randomized controlled trials are needed to determine the individual effects of exercise mode, duration, intensity, and frequency on fasting insulin levels in children because a larger body of evidence has found that these components influence glycemic control in adults. It should not be assumed that the physiologic response to these exercise moderators is similar in children, and future published research should provide a clear description of the exercise intervention (eg, intensity, duration, frequency).
frequency, attendance) to allow for a more thorough meta-regression analysis, with adequate statistical power to determine the influence of these potential moderators in pediatric populations. In addition, this analysis provides a quantitative estimate of the effect of exercise training and provides justification for including physical activity in interventions aimed at improving fasting insulin or IR. To provide the most accurate estimate of the effect of exercise training alone, interventions that combined diet and exercise components were excluded from our analysis only when an independent effect of exercise could not be estimated. Determining the effect of dietary modification in addition to exercise training was beyond the scope of the current review. However, health professionals and researchers would be remiss to not suggest dietary change in addition to regular exercise; well-designed lifestyle education involving a combination of diet and physical activity treatment therapies could provide health benefits beyond that of exercise alone.

**CONCLUSIONS**

Based on the cumulative results from peer-reviewed research published between 1999 and 2013, a small to moderate effect was found for exercise training improvements in fasting insulin levels and IR in children and adolescents. Measurable improvements in clinically relevant insulin outcomes (11.4 U/mL [95% CI: 5.2–17.5] and 2.0 [95% CI: 0.4–3.6] in fasting insulin and HOMA-IR, respectively) will help physicians and health care professionals implement research findings into patient treatment and disease prevention. Because this small to moderate effect in fasting insulin and IR in children and adolescents was consistent across gender, race, and age, our results suggest that this analysis is an accurate estimate of the magnitude of the effect in youth aged 6 to 19 years. Although the relatively small body of published literature did not allow for a thorough analysis of the effect of frequency, duration, intensity, mode, or volume of exercise, the beneficial effects of exercise training on fasting insulin and IR are clear. In the absence of a clear consensus on the most effective type of exercise for treating these outcomes, emphasis should be placed on ways to incorporate daily physical activity, in addition to “exercise training,” into the lives of children and adolescents, especially those at risk for developing obesity and diabetes.

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