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Exercise dose and diabetes risk in overweight and obese children: A randomized, controlled trial

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Abstract

Context—Pediatric studies showed that aerobic exercise reduces metabolic risk, but dose response information is not available.

Objective—Test the effect of aerobic training dose on insulin resistance, fatness, visceral fat, and fitness in overweight, sedentary children, and test moderation by sex and race.

Design, Setting, and Participants—Randomized, controlled, efficacy trial from 2003 through 2007, in which 222 overweight or obese, sedentary children (mean age, 9.4 yrs; 42% male, 58% black) were recruited from 15 public schools in the Augusta, GA area.

Intervention—Low-dose (20 min/d, n = 71) or high-dose (40 min/d, n = 73) aerobic training (13 ± 1.6 wk, 5 d/wk), or control condition (usual physical activity, n = 78); 94% retention.

Main outcome measures—Prespecified primary outcomes were type 2 diabetes risk at posttest, assessed by insulin area under the curve (AUC) from oral glucose tolerance test, aerobic fitness, percent body fat via dual-energy x-ray absorptiometry, and visceral fat via magnetic resonance, analyzed by intent-to-treat.

Results—Most children (85%) were obese. At baseline, the mean BMI was 26 (SD = 4.4). Reductions in insulin AUC were larger in the high-dose (adjusted mean difference [95% CI], −3.56 [−6.26 to −0.85], $P = .01$) than low-dose group (−2.96 [−5.69 to −0.22], $P = .03$) $\times 10^3$ μU/mL) vs control group. Dose-response trends were also observed for body fat (−1.4 [−2.2 to −0.7], P < .001; −0.8 [−1.6 to −0.07] %, P =.03) and visceral fat (−3.9 [−6.0 to −1.7], $P < .001$; −2.8 [−4.9 to −0.6] cm^3, $P = .01$) in the high- and low-dose vs control groups, respectively. Effects in the high- and low-dose groups vs control were similar for fitness (2.4 [0.4 to 4.5], $P = .02$; 2.4 [0.3 to 4.5] mL/kg/min, $P = .03$). High- vs. low-dose group effects were similar for these outcomes. There was no moderation by sex or race.

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Conclusions—Three months of 20 or 40 min/d aerobic training improved fitness, and demonstrated dose-response benefits on insulin resistance, general and visceral adiposity in sedentary, overweight or obese children, regardless of sex or race.

Trial Registration—Clinicaltrials.gov identifier: NCT00108901

Keywords

aerobic exercise; dose-response; insulin resistance; adiposity; fitness

INTRODUCTION

Child obesity and overweight are epidemic in US children.[1] A third of elementary-age children are overweight or obese.[2] Childhood obesity is associated with a number of adverse conditions formerly thought to occur only in adults, including type 2 diabetes and atherosclerosis.[3–7] Overweight, minority ethnicity, and family history of diabetes are risk factors for type 2 diabetes in youth.[8]

The Diabetes Prevention Program demonstrated reduction in diabetes risk among adults with prediabetes through diet and exercise.[9] Some dose-response relationships between exercise and metabolic risk have been demonstrated in adults.[10] Previous studies in children have shown reduction in metabolic risk factors through exercise,[11–13] but dose response information needed to formulate evidence-based public health recommendations for children is not available.[14,15–16]

The purpose of the study was to test the dose-response effect of an aerobic training program on insulin resistance, overall and visceral adiposity, and aerobic fitness in overweight children. A secondary aim was to test moderation by race and sex.

METHODS

Participants

Children were recruited from schools during 2003–2006 for a trial of aerobic exercise on health. The study was advertised via presentations and flyers distributed at 15 elementary schools in Richmond and Columbia counties in Georgia, and Aiken county in South Carolina. Inclusion criteria were: white or black (i.e. African-American) race, aged 7–11 years, overweight or obese (≥85th percentile body mass index, BMI),[17] sedentary (no regular physical activity program more than 1 hour per week), no medical condition or medications that would affect study results or limit physical activity, and able to provide a fasting blood sample at baseline. Informed consent and assent were obtained verbally and in writing from a parent or guardian and the child. The study was approved by the Human Assurance Committee of the Medical College of Georgia. Testing and intervention occurred at the Medical College of Georgia.

Procedure

Six cohorts of 30 to 40 children participated over 4 years. Randomization to a low-dose exercise treatment (20 min/d of aerobic exercise), a high dose exercise treatment (40/d of aerobic exercise) or a no treatment control condition was done by the statistician (JLW), stratified by race and sex. As each cohort was enrolled, each subject was assigned a uniform (0,1) random number using SAS within their respective race and sex group. If the number fell between 0 and 0.33 the subject was randomized to the low-dose group, between 0.34 and 0.67 the subject was randomized to the high-dose group, and above 0.67 the subject was randomized to the control group. Assignments were concealed until baseline testing was

completed, then communicated to the study coordinator, who enrolled and informed participants and monitored adverse events reported by participants. Children assigned to the control condition were asked to continue their usual activities. All families enrolled in the study were offered monthly lifestyle education classes that addressed topics such as healthy diet, physical activity, and stress management.

Exercise interventions

The aerobic exercise program was offered each day after school for 10 to 15 weeks during a school semester. Children were bused to a gymnasium at the Georgia Prevention Institute and offered healthy snacks prior to the exercise. The exercise conditions were equivalent in intensity, and differed only in duration and therefore volume (i.e., energy expenditure) of daily exercise. Children assigned to the high-dose exercise condition were offered two 20-min exercise bouts each school day. Children assigned to the low-dose exercise condition were included in the first 20-min bout in the gymnasium and then went to another room for a 20-min sedentary period.

The emphasis was on intensity, enjoyment, and safety, not competition nor skill enhancement. Activities were selected based on ease of comprehension, fun, and eliciting intermittent vigorous movement, and included running games, jump rope, and modified basketball and soccer (e.g., [18]). Points were awarded daily for an average heart rate >150 bpm in the program (S610i; Polar Electro, 30 s epoch) and redeemed for weekly prizes. The program handbook is available on request.

Measurements

The primary outcomes of the study included insulin resistance (i.e., insulin AUC), fatness, visceral fat, and aerobic fitness; fasting glucose was a secondary outcome. A secondary aim of the study tested moderation of group effects by race and sex, to determine generalizability of results. Exploratory outcomes included fasting insulin, Matsuda index, disposition indices, subcutaneous abdominal fat, and BMI z-score. Measurements were conducted at baseline and repeated at posttest, which was scheduled 1–3 days following the child's last exercise session to minimize acute effects. Children were scheduled for posttest in the order that they were tested at baseline, balanced by group assignment, to avoid confounding by time between baseline and posttest, or the duration of intervention. Most posttesting (e.g., blood tests, dual-energy x-ray absorptiometry, fitness) was completed in 2006; magnetic resonance posttesting was completed in 2007. Parents reported age, sex, race (black or white), ethnicity, and family history of diabetes in biological parents or grandparents.

Blood tests—The oral glucose tolerance test (OGTT) was used to measure diabetes risk at baseline and posttest.[19] Fasting glucose and insulin levels were determined by averaging serum samples at −15, −10, and −5 min prior to glucose ingestion (1.75 g/kg dextrose based on ideal body weight, up to 75 g). Serum samples were taken every 30 min for 2 h after glucose was consumed. Insulin area under the curve (AUC) was calculated via the trapezoidal rule. Glucose was measured using the glucose oxidase method (Analox), insulin using radioimmunoassay (human specific insulin, Linco Research Inc.). The mean intra-assay coefficients of variation (CV) for glucose and insulin assays are 0.61 and 4.5%, and interassay CV are 1.45 and 2.3%, respectively. Prediabetes was assessed by impaired fasting glucose (fasting plasma glucose 100–125 mg/dL) or impaired glucose tolerance (2-h glucose 140–199 mg/dL) at baseline.[20]

Insulin AUC was the prespecified primary outcome. Fasting glucose was a secondary outcome. Additional diabetes risk indices which were either validated in children[21] or demonstrated to predict the incidence of diabetes in adults[22] after the trial began were

calculated as exploratory outcomes. The Matsuda index of insulin sensitivity was calculated.[23,24] Beta-cell function was assessed in 2 ways. The disposition index based on the OGTT (DI_{OGTT}) was calculated as the product of the Matsuda index and insulinogenic index (i.e., $\Delta Insulin_{0\text{-}30}/\Delta Glucose_{0\text{-}30}$).[22,25] The disposition index based on fasting insulin (DI_{FI}) was the product of fasting $insulin^{-1}$ and the insulinogenic index.[21] Twenty-nine individuals were excluded from the analyses for insulin AUC and Matsuda index, and 6 from disposition indices, due to missing OGTT data points at baseline.

Estradiol was measured in girls by double-antibody radioimmunoassay, and testosterone in boys by coated-tube radioimmunoassay (Diagnostic Products Corp.). Intra- and interassay CV for estradiol are 3.6% and 5.2%, and for testosterone are 2.7% and 8.6%, respectively. Testosterone and estradiol values were normalized and combined into a composite variable to adjust potential effects of pubertal development on insulin resistance.

Body composition—Dual-energy X-ray absorptiometry (Hologic QDR-4500W) of the whole body was the primary body fat outcome. Abdominal visceral and subcutaneous fat content was measured with magnetic resonance images (1.5T, General Electric Medical Systems) of five 1 cm transverse slices around the L4–L5 disk.[26] Visceral fat was a primary outcome, and subcutaneous abdominal fat was an exploratory outcome.

Cardiovascular fitness—Cardiovascular fitness was determined using a multistage treadmill test modified from the protocol for poorly fit children (oxygen consumption [VO_2] relative to body mass, mL/kg/min, Sensormedics Vmax 229).[27,28] The modified protocol incorporated a warm-up period of 2.5 mph, 0% slope for 2 min before the warm-up at 3 mph, 3% slope for 2 min in the original protocol. After the warm-up, the speed remained at 3 mph and slope increased by 2% every 2 min until the child decided to stop, or until maximal oxygen consumption (VO_2 max) was reached. Because not all children attain VO_2 max, the peak VO_2 value during the treadmill test was utilized as the primary fitness outcome.

Anthropometrics—Anthropometrics were measured at least twice until consistent measures were obtained. BMI percentiles and z-scores were determined from body weight (in shorts and t-shirt; Detecto) and height (without shoes; HR100, Tanita).[17] BMI z-score was an exploratory outcome. Tanner stages were assessed by pediatricians.

Physical activity and energy intake—Physical activity was self-reported using questions from the Youth Risk Behavior Survey.[29,30] Moderate physical activity (d/wk) was determined by the question, ‘On how many of the past 7 days did you participate in physical activity for at least 30 min that did not make you sweat or breathe hard, such as fast walking, slow bicycling, skating, pushing a lawn mower or mopping floors?’ Vigorous physical activity (d/wk) was determined by the question, ‘On how many of the past 7 days did you exercise or participate in physical activity for at least 20 min that made you sweat or breathe hard, such as bicycling, fast dancing or similar aerobic activities?’

To assess compensation for energy expenditure in the exercise programs, three 24-hour diet recalls with food records were obtained to provide mean daily energy intake (kcal; Nutrition Data System for Research, software version 2006). Prior to the recall, the child and parent were trained in how to maintain a diet record using food models, portion booklets, and containers for estimating serving size.

Energy expenditure during aerobic training—Energy expenditure during the exercise sessions was estimated by first regressing VO_2 on heart rate from each treadmill test. The child’s mean slope between baseline and posttest was used to adjust for improved

fitness elicited by the intervention. Energy expenditure (EE, kcal) and intensity (metabolic equivalent, MET) in the exercise program was then estimated for 123 children (85% of those so assigned, who provided adequate data during treadmill tests) using daily attendance and average heart rate. A coefficient of 5 kcal/L was used for estimation of EE from VO_2.

Statistical Analyses

A planned sample size of 80/group, allowing for 20% attrition resulting in 64/group at posttest, was selected to provide ≥80% power using a 2-sided alpha level of 0.05 to detect group differences on most primary outcomes (insulin resistance and body fat, each 96%; visceral fat, 71%; and fitness, 98% power, respectively), based on results from prior studies which showed group differences in change on fasting insulin (−4.2 μU/mL), body fat (−1.6%),[12] visceral fat (−2.0 cm^3),[31] and fitness (+2.2 mL/kg/min).[32] All statistical analyses were performed using SAS 9.2 and a 2-sided alpha level of 0.05. Data were examined for normality and logarithmic transformations applied if necessary. Group differences at baseline were determined using analysis of variance and chi-square tests.

Repeated measures mixed models used maximum likelihood estimation and a Kenward-Rogers adjustment to the degrees of freedom for an intent-to-treat analysis of each outcome measure using all available data. Base models for each outcome measure included the fixed effects of group (control, low dose, and high dose) and measurement time (baseline or post-test) and their interaction, and controlled cohort, race, and sex. Subject nested within group was considered a random effect. The modeled covariance structure between measurement times was unstructured due to only having two measurement times. Other potential covariates included Tanner stages, sex hormones, and family history of diabetes at baseline. If either Tanner stage variable was significant, they were both included. Prespecified moderators (sex, race, and sex by race) were tested to determine generalizability, and exploratory moderators (family history of diabetes, prediabetes status) were tested to see if higher-risk groups were more likely to benefit, each controlling for covariates. Final models included effects in the base model, any statistically significant covariates, and any statistically significant interactions with group and measurement time. A priori linear contrasts across the three groups of the change from baseline to posttest tested dose-response effects of exercise intervention. Pairwise comparisons of change between groups were performed.

RESULTS

The participant flow diagram is presented in Figure 1. We randomized 222 children to control (N=78), low-dose (N=71), and high-dose (N=73) conditions. Similar baseline characteristics were observed in the 3 groups (Table 1). A majority of children (85%) were obese, and 28% had prediabetes.

The number of minor adverse events that occurred during testing were similar between groups (5, 7, 6 in control, low-dose, high-dose groups, respectively, P = .85). The time between baseline and posttest was similar among control, low-, and high-dose groups (mean (SD), 129 (19), 129 (15), 128 (13), $P = .91$). Intervention data, including adherence, are presented in Table 2. Duration of intervention, number of minor adverse events during intervention, attendance, heart rate, and intensity were similar. There was one serious adverse event (foot fracture in the low-dose group). As expected, daily and total EE were higher in the high- vs. low-dose group. Ninety-four percent of the sample (N = 209) was retained at posttest. No effect of group was observed on dietary intake or physical activity self-reports. Significant covariates included Tanner stages for insulin AUC, Matsuda index, fasting insulin and glucose, and sex hormones for body fat.

Primary outcomes: Insulin resistance, fatness, and fitness

Changes on outcomes by exercise dose are depicted in Figure 2. Significant downward linear dose-response trends, with larger reductions between baseline and posttest for the high-dose than control group, were observed for insulin AUC (adjusted mean difference [95% CI], −3.56 [−6.26 to −0.85] μU/mL×10^3, P = .01), body fat (−1.4 [−2.2 to −0.7]%, P < .001), and visceral fat (−3.9 [−6.0 to −1.7] cm^3, P < .001). Reductions in the low-dose group, which were larger than changes in the control group, were also observed for these outcomes (−2.96 [−5.69 to −0.22] μU/mL×10^3, P = .03; −0.8 [−1.6 to −0.07] %, P =.03; −2.8 [−4.9 to −0.6] cm^3, P = .01, respectively). Although mean adjusted differences in change were larger in the high- vs low-dose group for these outcomes, the difference in changes between the exercise groups was not significant. Very similar increases for both exercise groups were observed for fitness, with each group's change being significantly larger than that of the control condition (2.4 [0.4 to 4.5], P =.02; 2.4 [0.3 to 4.5] mL/kg/min, P = .02 in the high- and low-dose vs control groups, respectively), with no significant difference between exercise doses. Table 3 presents the adjusted mean differences between groups in change from baseline to posttest with corresponding 95% confidence intervals, and P values for trend and pairwise comparisons from intent-to-treat analyses.

Other outcomes

No significant effect of exercise was detected for the secondary outcome, fasting glucose. Dose-response benefits of exercise were indicated by significant downward trends across groups (high-dose vs control, low-dose vs control, respectively) for fasting insulin (adjusted mean difference [95% CI], −3.98 [−7.04 to −0.91], P =.01; −3.55 [−6.67 to −0.43] μU/mL, P = .03), and subcutaneous abdominal fat (−24 [−32 to −15], P < .0001; −15 [−24 to −7] cm^3, P = .0006). For BMI z-score, there was a significant downward trend and differences in change were observed for the high-dose group vs other groups (−0.1 [−0.14 to −0.05], P < .0001 vs control group; −0.05 [−0.10 to −0.01], P =.02 vs low-dose group), but there was no difference in effect between low-dose and control groups.

A significant upward trend with exercise dose was seen on the Matsuda index (0.67 [0.26 to 1.08], P = .002; 0.56 [0.14 to 0.97], P = .009). An upward trend and difference in change between high-dose and control groups was shown for DI_{OGTT} (0.84 [0.02 to 1.65], P = .04), but the changes in the low-dose group were similar to the high-dose and control group. No group difference in change was detected for DI_{FI}.

For fasting insulin, a significant interaction of family history of diabetes by group by time was found (data not shown). However, excluding an extreme fasting insulin value at posttest (136 μU/mL) without excluding other data for that child (in control group with no family history of diabetes) eliminated the interaction. Results are presented with all data in Figure 2 and Table 3, and in Table 3 also with the extreme value excluded, which eliminated the difference in change between the low-dose and control groups. There were no other significant interactions of group by time with family history, nor with race, sex, or prediabetes status.

COMMENT

This randomized clinical trial with exceptional adherence and retention quantified the efficacy of monitored aerobic exercise training to reduce diabetes risk (i.e., insulin resistance) and other indices of cardiometabolic risk in sedentary, overweight and obese children, 28% of whom had prediabetes. A daily aerobic exercise intervention over 3 mo. showed clear dose-response benefits reducing diabetes risk, as assessed by insulin response to OGTT, fasting insulinsurrogate indices of diabetes risk integrating insulin resistance and β-cell function. The high-dose exercise intervention demonstrated significant benefit on the

DI_{OGTT}, a surrogate index of diabetes risk integrating insulin resistance and β-cell function, which is an excellent predictor of diabetes incidence in adults.[22,33] The reductions in fasting insulin moved most participants in the exercise groups from a high to a borderline high clinical category for insulin resistance.[34] No intervention effects were detected on fasting glucose or the DI_{FI}. Dose-response improvements in detailed measures of fatness were observed, and the two exercise doses showed similar improvements on fitness. This extends the literature with quantified benefits, including weight loss, from closely monitored, selected doses of aerobic training with no dietary restrictions. No evidence for EE compensation was provided.

No difference in efficacy was noted between boys and girls, black and white children, or children with prediabetes vs normoglycemic children. These consistent effects of intervention do not conflict with cross-sectional race differences reported in the literature (lower visceral adiposity, greater insulin resistance, and higher disposition index in black children),[35–37] but it contrasts with the prospective finding that black girls are less sensitive than white girls to the effects of physical activity on fat accretion.[38] An effect modification for the effect of exercise on fasting insulin was detected for family history, but this appeared to be due to one extreme value, probably due to noncompliance with fasting. Therefore the cardiometabolic effects of exercise appear to be generalizable to overweight black and white boys and girls, regardless of prediabetes or family history of diabetes.

The increment of benefit between the control and low-dose conditions was larger than the additional benefit observed between low-and high-dose groups. The greatest benefit is obtained from a given amount of physical activity in the most sedentary people, with smaller benefits accruing to people who are already moderately active.[39] The low- and high-dose groups showed nearly identical effects on fitness. A similar result on insulin resistance was obtained by the STRRIDE study, where the low-volume, moderate intensity group improved more than a similar volume, high intensity group, and had similar improvement to the high-volume, high-intensity group. Moderate as well as vigorous activity was linked with insulin sensitivity in a population study.[40] Inflammation from a large volume or high intensity of exercise may impair insulin sensitivity.[41] Fitness benefits may be gained based on intensity rather than volume of exercise.[42] This study was powered to detect a dose-response gradient but was unable to distinguish between these daily volumes of aerobic activity, except for subcutaneous abdominal fat and BMI z-score, for which greater benefits were observed with 40 than 20 min daily vigorous activity.

Though several exercise studies have now utilized an 8–9 month training period, more than twice that of the current study, the 5 day/wk frequency in this study is rare.[43] The Cochrane review of obesity treatment trials[44] includes only 9 focused on physical activity in children under 12, and only 1 of comparable size (N = 218). In the larger studies, interventions consisted of clinical advice rather than monitored exercise. Most interventions were of similar or shorter duration. Physical activity interventions were of lower intensity and frequency (contacts with subjects from 1/mo to 3/wk) and few isolated exercise rather than combining it with dietary intervention. Nonetheless, the relatively short duration of intervention, and lack of follow-up assessment of possible lasting effects, are limitations of the current study. There were other limitations. Participants were not blinded to condition, because it was a behavioral intervention. Measurement staff were not blinded. The control group was not offered an attention-control intervention program; daily attention from adults and the minimal nutrition intervention may have affected outcomes in the exercise groups.

Large, well-conducted school-based studies have tested effects of physical activity on obesity in children, and have failed to reduce obesity, perhaps due to inadequate dose;[45,46] one succeeded only in girls.[47] The HEALTHY study was designed to reduce risk for type 2

diabetes using multiple school-wide strategies to improve nutrition and physical activity over 3 years; it improved adiposity measures and fasting insulin by a small amount. This efficacy study, with a more intensive, focused intervention, achieved 3X the effect on BMI z-score and 8X the effect on fasting insulin in overweight children in a short time. These results contrast with a similar exercise intervention in black girls that despite longer duration (10 mo.) and improved adiposity and fitness, did not reduce fasting insulin concentration.[11] That study did not restrict enrollment to overweight or obese children, who are more insulin resistant and may be more sensitive to intervention than normal weight peers.

Twenty minutes of aerobic exercise per school day over just a few months showed benefits over the control condition on insulin resistance, fitness, and fatness. Thus, measurable health benefits could be achieved through a daily dose of safe, vigorous physical activity which could be achieved during the school day by providing daily fitness-focused physical education classes, recess, and other physical activity opportunities.[48–52] However, to achieve the benefits of 40 min/d of vigorous physical activity (the basis for the 60 min/d recommendation for physical activity for free-living children),[14] after-school physical activity programs may be necessary. Schools are the logical focus for such public health interventions.[49] An ancillary study showed benefits of the exercise intervention on cognition and mathematics achievement, which may increase its appeal to educators.[53] Inclusive, appealing interventions with fun, simple games that minimize barriers to participation will be most effective. Using heart rate as a physiological index of effort and providing contingent rewards for such exertion, rather than athletic performance, encourages even unfit children to exercise intensely enough to improve fitness and improve energy balance.

CONCLUSIONS

Clear benefits of 3 mo of 20 or 40 min/d aerobic training on diabetes risk (insulin resistance, β-cell function), fitness, general and visceral adiposity were observed in sedentary, overweight or obese children regardless of race or sex, with a dose-response gradient for insulin resistance and adiposity.

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CLD designed and oversaw the study, analysis, and interpretation of data, drafted the article, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. NKP and BAD assisted with analysis and drafting the article. JLW randomized participants and analyzed data. JDA assisted with design, oversaw acquisition of magnetic resonance data, and assisted with drafting the article. RB provided medical oversight, and assisted with design and interpretation. AM assisted with analysis, interpretation, and drafting the article. CAB assisted with design and oversaw acquisition of data and intervention. BAG assisted with design and interpretation, and oversaw biochemical assays. All authors revised and approved the final version.

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References

1. Strauss RS, Pollack HA. Epidemic increase in childhood overweight, 1986–1998. JAMA. Dec 12; 2001 286(22):2845–2848. [PubMed: 11735760]
2. Ogden CL, Carroll MD, Curtin LR, Lamb MM, Flegal KM. Prevalence of high body mass index in US children and adolescents, 2007–2008. JAMA. Jan 20; 2010 303(3):242–249. [PubMed: 20071470]
3. Davis CL, Kapuku G, Snieder H, Kumar M, Treiber FA. Insulin resistance syndrome and left ventricular mass in healthy young people. Am J Med Sci. Aug; 2002 324(2):72–75. [PubMed: 12186110]
4. Davis CL, Flickinger B, Moore D, Bassali R, Domel Baxter S, Yin Z. Prevalence of cardiovascular risk factors in schoolchildren in a rural Georgia community. Am J Med Sci. Aug; 2005 330(2):53–59. [PubMed: 16103784]
5. Pinhas-Hamiel O, Dolan LM, Daniels SR, Standiford D, Khoury PR, Zeitler P. Increased incidence of non-insulin-dependent diabetes mellitus among adolescents. J Pediatr. 1996; 128(5 Pt 1):608–615. [PubMed: 8627431]
6. McGill HC Jr, McMahan CA, Zieske AW, et al. Association of coronary heart disease risk factors with microscopic qualities of coronary atherosclerosis in youth. Circulation. 2000; 102(4):374–379. [PubMed: 10908207]
7. Daniels SR, Arnett DK, Eckel RH, et al. Overweight in children and adolescents: pathophysiology, consequences, prevention, and treatment. Circulation. Apr 19; 2005 111(15):1999–2012. [PubMed: 15837955]
8. American Diabetes Association. Type 2 diabetes in children and adolescents. Diabetes Care. Mar; 2000 23(3):381–389. [PubMed: 10868870]
9. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. Feb 7; 2002 346(6):393–403. [PubMed: 11832527]
10. Johnson JL, Slentz CA, Houmard JA, et al. Exercise training amount and intensity effects on metabolic syndrome (from Studies of a Targeted Risk Reduction Intervention through Defined Exercise). Am J Cardiol. Dec 15; 2007 100(12):1759–1766. [PubMed: 18082522]
11. Barbeau P, Johnson MH, Howe CA, et al. Ten months of exercise improves general and visceral adiposity, bone, and fitness in black girls. Obesity (Silver Spring). Aug; 2007 15(8):2077–2085. [PubMed: 17712126]
12. Ferguson MA, Gutin B, Le NA, et al. Effects of exercise training and its cessation on components of the insulin resistance syndrome in obese children. Int J Obes Relat Metab Disord. Aug; 1999 23(8):889–895. [PubMed: 10490792]
13. Gutin B, Owens S, Okuyama T, Riggs S, Ferguson M, Litaker M. Effect of physical training and its cessation on percent fat and bone density of children with obesity. Obes Res. Mar; 1999 7(2): 208–214. [PubMed: 10102258]
14. Strong WB, Malina RM, Blimkie CJ, et al. Evidence based physical activity for school-age youth. J Pediatr. Jun; 2005 146(6):732–737. [PubMed: 15973308]
15. Institute of Medicine. Adequacy of evidence for physical activity guidelines development: Workshop summary. Washington, DC: The National Academies Press; 2007.
16. Glickman, D.; Parker, L.; Sim, LJ.; Cook, HDV.; Miller, EA., editors. Institute of Medicine. Accelerating Progress in Obesity Prevention: Solving the Weight of the Nation. Washington, DC: The National Academies Press; 2012. http://www.iom.edu/Reports/2012/Accelerating-Progress-in-Obesity-Prevention.aspx
17. Ogden CL, Kuczmarski RJ, Flegal KM, et al. Centers for Disease Control and Prevention 2000 growth charts for the United States: Improvements to the 1977 National Center for Health Statistics version. Pediatrics. Jan; 2002 109(1):45–60. [PubMed: 11773541]
18. Howe CA, Freedson PS, Feldman HA, Osganian SK. Energy Expenditure and Enjoyment of Common Children's Games in a Simulated Free-Play Environment. J Pediatr. Dec; 2010 157(6): 936-942.e931–932. [PubMed: 20708746]

19. Yeni-Komshian H, Carantoni M, Abbasi F, Reaven GM. Relationship between several surrogate estimates of insulin resistance and quantification of insulin-mediated glucose disposal in 490 healthy nondiabetic volunteers. Diabetes Care. 2000; 23(2):171–175. [PubMed: 10868826]
20. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care. 1997; 20:1183–1197. [PubMed: 9203460]
21. Sjaarda LG, Bacha F, Lee S, Tfayli H, Andreatta E, Arslanian S. Oral Disposition Index in Obese Youth from Normal to Prediabetes to Diabetes: Relationship to Clamp Disposition Index. J Pediatr. Jul; 2012 161(1):51–57. [PubMed: 22325254]
22. Abdul-Ghani MA, Williams K, DeFronzo RA, Stern M. What is the best predictor of future type 2 diabetes? Diabetes Care. Jun; 2007 30(6):1544–1548. [PubMed: 17384342]
23. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. Diabetes are. Sep; 1999 22(9):1462–1470.
24. Yeckel CW, Weiss R, Dziura J, et al. Validation of insulin sensitivity indices from oral glucose tolerance test parameters in obese children and adolescents. J Clin Endocrinol Metab. Mar; 2004 89(3):1096–1101. [PubMed: 15001593]
25. Hanson RL, Pratley RE, Bogardus C, et al. Evaluation of simple indices of insulin sensitivity and insulin secretion for use in epidemiologic studies. Am J Epidemiol. 2000; 151(2):190–198. [PubMed: 10645822]
26. Owens S, Gutin B, Ferguson M, Allison J, Karp W, Le NA. Visceral adipose tissue and cardiovascular risk factors in obese children. J Pediatr. Jul; 1998 133(1):41–45. [PubMed: 9672508]
27. Rowland, TW. Aerobic Exercise Testing Protocols. Champaign, IL: Human Kinetics; 1993.
28. American College of Sports Medicine. ACSM's guidelines for exercise testing and prescription. 6. Baltimore: Lippincott Williams & Wilkins; 2000.
29. Brener ND, Kann L, Kinchen SA, et al. Methodology of the youth risk behavior surveillance system. MMWR. Recommendations and reports: Morbidity and mortality weekly report. Recommendations and reports/Centers for Disease Control. Sep 24; 2004 53(RR-12):1–13.
30. Brener ND, Collins JL, Kann L, Warren CW, Williams BI. Reliability of the Youth Risk Behavior Survey Questionnaire. Am J Epidemiol. Mar 15; 1995 141(6):575–580. [PubMed: 7900725]
31. Owens S, Gutin B, Allison J, et al. Effect of physical training on total and visceral fat in obese children. Med Sci Sports Exerc. Jan; 1999 31(1):143–148. [PubMed: 9927022]
32. Gutin B, Yin Z, Humphries MC, Barbeau P. Relations of moderate and vigorous physical activity to fitness and fatness in adolescents. Am J Clin Nutr. Apr; 2005 81(4):746–750. [PubMed: 15817847]
33. Utzschneider KM, Prigeon RL, Faulenbach MV, et al. Oral disposition index predicts the development of future diabetes above and beyond fasting and 2-h glucose levels. Diabetes Care. Feb; 2009 32(2):335–341. [PubMed: 18957530]
34. Williams CL, Hayman LL, Daniels SR, et al. Cardiovascular health in childhood: A statement for health professionals from the Committee on Atherosclerosis, Hypertension, and Obesity in the Young (AHOY) of the Council on Cardiovascular Disease in the Young, American Heart Association. Circulation. Jul 2; 2002 106(1):143–160. [PubMed: 12093785]
35. Liese AD, D'Agostino RB Jr, Hamman RF, et al. The burden of diabetes mellitus among US youth: prevalence estimates from the SEARCH for Diabetes in Youth Study. Pediatrics. Oct; 2006 118(4):1510–1518. [PubMed: 17015542]
36. D'Adamo E, Northrup V, Weiss R, et al. Ethnic differences in lipoprotein subclasses in obese adolescents: importance of liver and intraabdominal fat accretion. Am J Clin Nutr. Sep; 2010 92(3):500–508. [PubMed: 20573788]
37. Gower BA, Nagy TR, Trowbridge CA, Dezenberg C, Goran MI. Fat distribution and insulin response in prepubertal African American and white children. Am J Clin Nutr. 1998; 67:821–827. [PubMed: 9583837]
38. White J, Jago R. Prospective associations between physical activity and obesity among adolescent girls: Racial differences and implications for prevention, physical activity and obesity among girls. Arch Pediatr Adol Med. Jun 1; 2012 166(6):522–527.

39. Haskell WL. Physical activity in the prevention and management of coronary heart disease. PCPFS Research Digest. 1995; 2(1):1–12.
40. Mayer-Davis EJ, D'Agostino R Jr, Karter AJ, et al. Intensity and amount of physical activity in relation to insulin sensitivity: The Insulin Resistance Atherosclerosis Study. JAMA. 1998; 279(9): 669–674. [PubMed: 9496984]
41. Suzuki K, Nakaji S, Yamada M, Totsuka M, Sato K, Sugawara K. Systemic inflammatory response to exhaustive exercise. Cytokine kinetics. Exerc Immunol Rev. 2002; 8:6–48. [PubMed: 12690937]
42. Gutin B, Barbeau P, Owens S, et al. Effects of exercise intensity on cardiovascular fitness, total body composition, and visceral adiposity of obese adolescents. Am J Clin Nutr. May; 2002 75(5): 818–826. [PubMed: 11976154]
43. Kesten JM, Griffiths PL, Cameron N. A systematic review to determine the effectiveness of interventions designed to prevent overweight and obesity in pre-adolescent girls. Obes Rev. Dec; 2011 12(12):997–1021. [PubMed: 21848919]
44. Oude Luttikhuis H, Baur L, Jansen H, et al. Interventions for treating obesity in children. Cochrane Database Syst Rev. 2009; (1):CD001872. [PubMed: 19160202]
45. Webber LS, Osganian SK, Feldman HA, et al. Cardiovascular risk factors among children after a 2 1/2-year intervention-The CATCH Study. Prev Med. 1996; 25(4):432–441. [PubMed: 8818067]
46. Sallis JF, McKenzie TL, Alcaraz JE, Kolody B, Hovell MF, Nader PR. Project SPARK. Effects of physical education on adiposity in children. Ann N Y Acad Sci. Oct 29.1993 699:127–136. [PubMed: 8267303]
47. Gortmaker SL, Peterson K, Wiecha J, et al. Reducing obesity via a school-based interdisciplinary intervention among youth: Planet Health. Arch Pediatr Adolesc Med. Apr; 1999 153(4):409–418. [PubMed: 10201726]
48. Sallis JF, McKenzie TL, Alcaraz JE, Kolody B, Faucette N, Hovell MF. The effects of a 2-year physical education program (SPARK) on physical activity and fitness in elementary school students. Sports, Play and Active Recreation for Kids. Am J Public Health. Aug; 1997 87(8):1328–1334. [PubMed: 9279269]
49. Pate RR, Davis MG, Robinson TN, Stone EJ, McKenzie TL, Young JC. Promoting Physical activity in children and youth. A leadership role for schools. A scientific statement from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism (Physical Activity Committee) in collaboration with the Councils on Cardiovascular Disease in the Young and Cardiovascular Nursing. Circulation. Aug 14; 2006 114(11):1214–1224. [PubMed: 16908770]
50. Donnelly JE, Greene JL, Gibson CA, Smith BK, Washburn RA, Sullivan DK, DuBose K, Mayo MS, Schmelzle H, Ryan JJ, Jacobsen DJ, Williams SL. Physical Activity Across the Curriculum (PAAC): a randomized controlled trial to promote physical activity and diminish overweight and obesity in elementary school children. Prev Med. Oct; 2009 49(4):336–341. [PubMed: 19665037]
51. Mahar MT, Murphy SK, Rowe DA, Golden J, Shields AT, Raedeke TD. Effects of a classroom-based program on physical activity and on-task behavior. Med Sci Sports Exerc. Dec; 2006 38(12):2086–2094. [PubMed: 17146314]
52. Kibbe DL, Hackett J, Hurley M, et al. Ten Years of TAKE 10!((R)): Integrating physical activity with academic concepts in elementary school classrooms. Prev Med. Jun 1; 2011 52 (Suppl 1):S43–50. [PubMed: 21281670]
53. Davis CL, Tomporowski PD, McDowell JE, et al. Exercise improves executive function and achievement and alters brain activation in overweight children: a randomized, controlled trial. Health Psychol. Jan; 2011 30(1):91–98. [PubMed: 21299297]

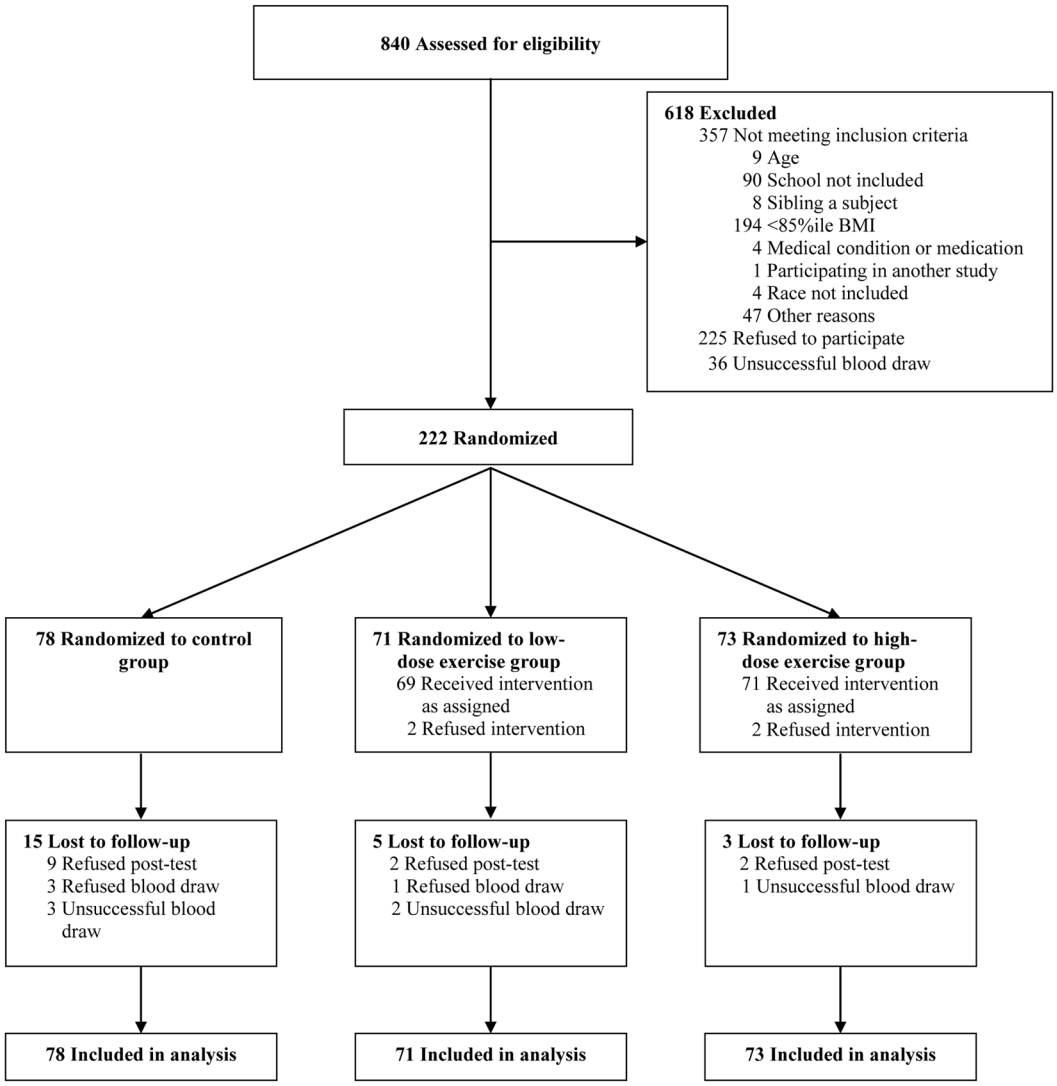

Figure 1.
Flow diagram for fasting blood samples.

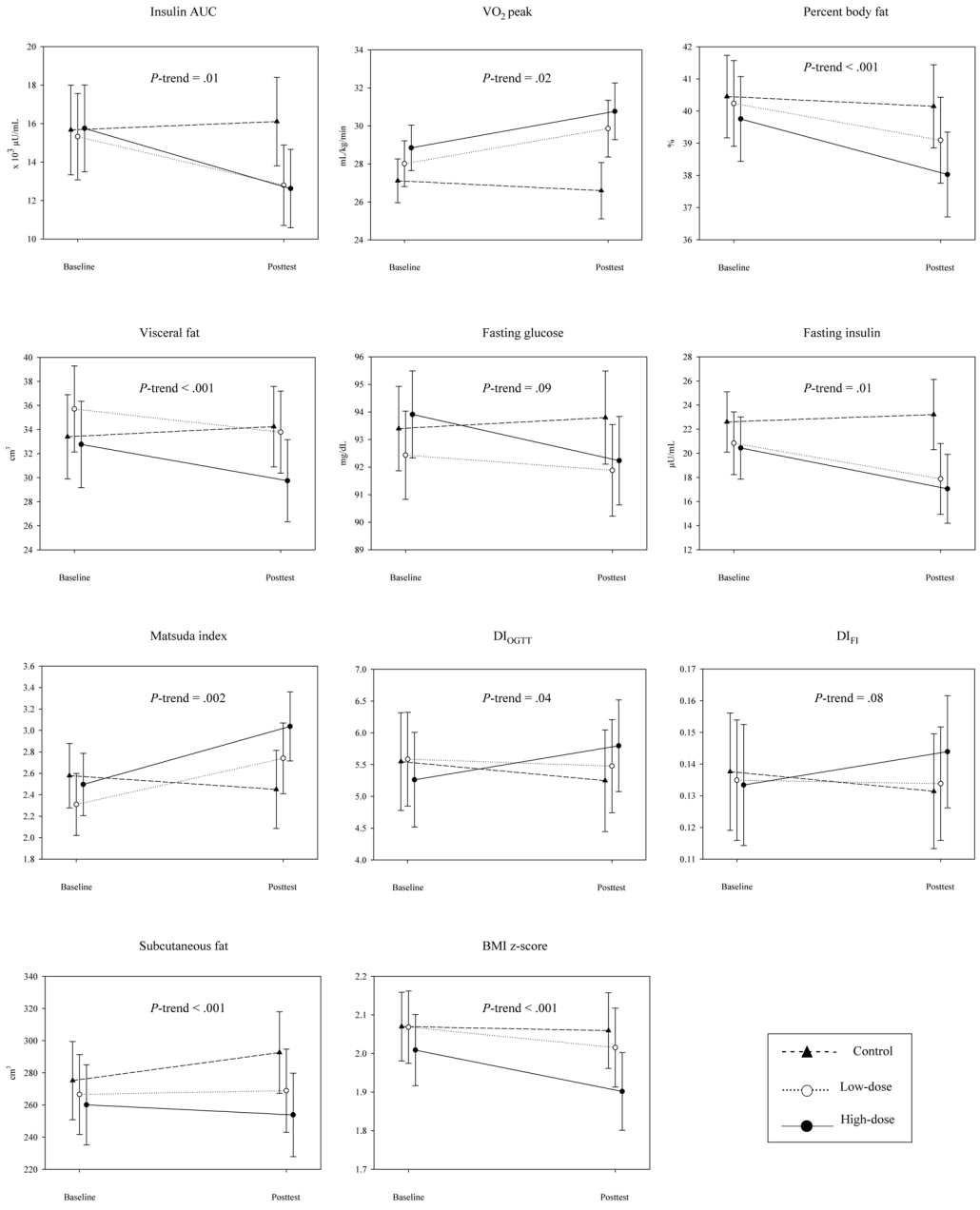

Figure 2.

Error bars indicate 95% confidence intervals. Data from intent-to-treat mixed-model repeated-measures analysis of variance of the effect of group on outcomes. The *P* value in each panel indicates the test of the dose-response trend, i.e. whether change between baseline and posttest differed between control and high-dose (40 min/day) exercise groups.

Table 1

Baseline characteristics of the participants[a]

	Total	Control	Low-dose exercise	High-dose exercise
No.	222	78	71	73
Categorical variables, No. (%)				
Male	94 (42)	30 (38)	31 (44)	33 (45)
Black	129 (58)	43 (55)	42 (59)	44 (60)
Hispanic	6 (3)	0 (0)	3 (4)	3 (4)
Family history of diabetes	134 (60)	49 (63)	41 (58)	44 (60)
Prediabetes	63 (28)	20 (26)	19 (27)	24 (33)
Obesity[b]	188 (85)	67 (86)	60 (85)	61 (84)
Severe obesity[c]	70 (32)	24 (31)	28 (39)	18 (25)
Tanner stage[d]				
Thelarche or gonadarche				
I	164 (74)	57 (73)	53 (75)	54 (74)
II	28 (13)	10 (13)	9 (13)	9 (12)
III	25 (11)	7 (9)	8 (11)	10 (14)
IV	4 (2)	4 (5)	0 (0)	0 (0)
V	1 (0)	0 (0)	1 (1)	0 (0)
Adrenarche				
I	158 (71)	55 (71)	52 (73)	51 (70)
II	43 (20)	14 (18)	12 (17)	17 (23)
III	17 (8)	8 (10)	5 (7)	4 (5)
IV	4 (2)	1 (1)	2 (3)	1 (1)
V	0 (0)	0 (0)	0 (0)	0 (0)
Continuous variables, mean (SD)				
Age, y	9.4 (1.1)	9.4 (1.1)	9.3 (0.9)	9.4 (1.2)
Insulin AUC, $\times 10^3$ μU/mL	16.3 (10.7)	16.3 (9.7)	16.1 (9.5)	16.4 (12.8)
VO_2 peak, mL/kg/min	27.6 (5.5)	26.8 (4.8)	27.8 (5.5)	28.5 (6.0)
Percent body fat	40.5 (6.2)	40.7 (6.8)	40.6 (6.1)	40.2 (5.7)
Visceral fat, cm^3	33.4 (16.2)	33.0 (16.7)	35.1 (16.9)	32.2 (15.1)
Fasting glucose, mg/dL	92.9 (7.8)	93.4 (8.3)	91.9 (6.3)	93.4 (8.5)
Fasting insulin, μU/mL	21.9 (12.4)	23.1 (14.2)	21.5 (11.1)	21.1 (11.5)
Matsuda index	2.4 (1.4)	2.5 (1.7)	2.2 (1.0)	2.4 (1.3)
DI_{OGTT}	5.6 (3.3)	5.5 (3.3)	5.8 (3.6)	5.4 (3.1)
DI_{FI}	0.14 (0.09)	0.14 (0.09)	0.14 (0.09)	0.14 (0.08)
Subcutaneous fat, cm^3	275 (109)	282 (116)	275 (104)	267 (107)
BMI z-score	2.1 (0.4)	2.1 (0.4)	2.1 (0.4)	2.0 (0.4)
BMI, kg/m^2	25.9 (4.4)	26.3 (4.6)	25.9 (4.1)	25.6 (4.5)
BMI percentile	97 (3.0)	97 (3.2)	97 (2.8)	97 (3.0)
Estradiol in girls, pg/mL	5.4 (9.1)	5.7 (6.8)	6.0 (13.7)	4.5 (4.9)

	Total	Control	Low-dose exercise	High-dose exercise
Testosterone in boys, ng/dL	18 (25)	22 (35)	17 (25)	16 (10)
Energy intake, kcal/d	1660 (500)	1730 (500)	1660 (500)	1600 (500)
Physical activity, d/wk				
Moderate	2 (2)	2 (2)	2 (2)	2 (2)
Vigorous	3 (2)	3 (2)	4 (3)	3 (2)

Abbreviations: AUC, area under the curve; VO_2, oxygen consumption; BMI, body mass index; DI_{OGTT}, disposition index based on oral glucose tolerance test measurement of insulin sensitivity (Matsuda index × insulinogenic index); and DI_{FI}, disposition index based on fasting estimate of insulin sensitivity (1/fasting insulin × insulinogenic index).

SI conversion factors: To convert glucose to mmol/L, multiply by 0.0555. To convert insulin to pmol/L, multiply by 6.945.

[a] No significant group differences ($P > 0.05$).

[b] Obese: BMI percentile ≥95.

[c] Severe obesity: BMI percentile ≥99.

[d] Percentages may not total to 100 due to rounding.

SI conversion factor: To convert energy intake to J/d, multiply by 4186.8. To convert estradiol to pmol/L, multiply by 3.671. To convert testosterone to nmol/L, multiply by 0.0347.

Table 2

Measures obtained during intervention

	Low-dose exercise	High-dose exercise	*P*
Minor adverse events, No.	31	35	.62
Continuous variables, mean (SD)			
Duration of intervention, wk	13 (1.5)	13 (1.7)	.93
Attendance, %	85 (12)	84 (14)	.88
Daily average heart rate, bpm	166 (7)	165 (9)	.37
Intensity, MET[a]	7.5 (1.4)	7.5 (1.4)	.94
Daily energy expenditure, kcal/d[a]	134 (24)	269 (70)	<.001
Total energy expenditure, kcal[a]	6727 (1719)	13025 (4144)	<.001

SI conversion factor: To convert energy expenditure to J or J/d, multiply by 4186.8.

[a]Intensity and energy expenditure were estimated from daily attendance and heart rate measures, using the mean slope of VO_2 regressed on heart rate from each child's treadmill tests at baseline and posttest.

Table 3

Changes in Diabetes Risk, Fitness, and Fatness Outcomes [a]

	Difference, Low-dose vs. Control	*P*, Low-dose vs. Control	Difference, High-dose vs Low-dose	*P*, High-dose vs Low-dose	Difference, High-dose vs Control	*P*, Trend, High-dose vs Control[b]
Primary outcomes						
Insulin AUC, × 10^3 μU/mL[c]	−2.96 (−5.69 to −0.22)	.03	−0.6 (−3.14 to 1.93)	.64	−3.56 (−6.26 to −0.85)	.01
VO_2 peak, mL/kg/min	2.37 (0.28 to 4.45)	.03	0.08 (−2.02 to 2.17)	.94	2.44 (0.36 to 4.53)	.02
Percent body fat[d]	−0.84 (−1.61 to −0.07)	.03	−0.58 (−1.34 to 0.18)	.13	−1.42 (−2.18 to −0.66)	<.001
Visceral fat, cm^3	−2.77 (−4.91 to −0.63)	.01	−1.09 (−3.23 to 1.05)	.32	−3.86 (−5.98 to −1.73)	<.001
Secondary outcome						
Fasting glucose, mg/dL[c]	−0.95 (−3.38 to 1.48)	.44	−1.13 (−3.51 to 1.26)	.35	−2.08 (−4.47 to 0.31)	.09
Exploratory outcomes						
Fasting insulin, μU/mL[c, e] ALL	−3.55 (−6.67 to −0.43)	.03	−0.43 (−3.46 to 2.60)	.78	−3.98 (−7.04 to −0.91)	.01
Fasting insulin, μU/mL[c,f] Extreme value excluded	−2.61 (−5.58 to 0.36)	.08	−.45 (−3.35 to 2.46)	.76	−3.05 (−5.98 to −0.13)	.04
Matsuda index[c]	0.56 (0.14 to 0.97)	.009	0.11 (−0.27 to 0.49)	.56	0.67 (0.26 to 1.08)	.002
DI_{OGTT}	0.19 (−0.63 to 1.02)	.65	0.64 (−0.12 to 1.4)	.10	0.84 (0.02 to 1.65)	.04
DI_{FI}	0.01 (−0.01 to 0.02)	.60	0.01 (−0.01 to 0.03)	.22	0.02 (0 to 0.04)	.08
Subcutaneous fat, cm^3	−15.1 (−23.7 to −6.53)	<.001	−8.62 (−17.2 to −0.08)	.048	−23.7 (−32.3 to −15.2)	<.001
BMI z-score	−0.04 (−0.09 to 0.00)	.06	−0.05 (−0.01 to −0.10)	.02	−0.10 (−0.14 to −0.05)	<.001

Abbreviations: AUC, area under the curve; VO_2, oxygen consumption; BMI, body mass index; DI_{OGTT}, disposition index based on oral glucose tolerance test measurement of insulin sensitivity (Matsuda index × insulinogenic index); and DI_{FI}, disposition index based on fasting estimate of insulin sensitivity (1/fasting insulin × insulinogenic index).

SI conversion factors: To convert glucose to mmol/L, multiply by 0.0555. To convert insulin to pmol/L, multiply by 6.945.

[a] Differences between groups in change from baseline to post [mean (95% CI)] adjusted for cohort, sex, and race.

[b] Test of linear trend is equivalent to test of high-dose vs. control group.

[c] Additionally adjusted for Tanner stages.

[d] Additionally adjusted for sex hormone level.

[e] All data.

[f] All cases with one extreme value in control group excluded.