

Exercise Dose and Diabetes Risk in Overweight and Obese Children

A Randomized Controlled Trial

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CHILD OBESITY AND OVERweight are epidemic in US children.¹ A third of elementary school-aged 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 race/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.¹⁴⁻¹⁶

The purpose of the current 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

Context Pediatric studies have shown that aerobic exercise reduces metabolic risk, but dose-response information is not available.

Objectives To test the effect of different doses of aerobic training on insulin resistance, fatness, visceral fat, and fitness in overweight, sedentary children and to test moderation by sex and race.

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

Intervention Children were randomly assigned to low-dose (20 min/d; n=71) or high-dose (40 min/d; n=73) aerobic training (5 d/wk; mean duration, 13 [SD, 1.6] weeks) or a control condition (usual physical activity; n=78).

Main Outcome Measures The prespecified primary outcomes were postintervention type 2 diabetes risk assessed by insulin area under the curve (AUC) from an oral glucose tolerance test, aerobic fitness (peak oxygen consumption [$\dot{V}O_2$]), percent body fat via dual-energy x-ray absorptiometry, and visceral fat via magnetic resonance, analyzed by intention to treat.

Results The study had 94% retention (n=209). Most children (85%) were obese. At baseline, mean body mass index was 26 (SD, 4.4). Reductions in insulin AUC were larger in the high-dose group (adjusted mean difference, -3.56 [95% CI, -6.26 to -0.85] $\times 10^3$ $\mu\text{U/mL}$; $P=.01$) and the low-dose group (adjusted mean difference, -2.96 [95% CI, -5.69 to -0.22] $\times 10^3$ $\mu\text{U/mL}$; $P=.03$) than the control group. Dose-response trends were also observed for body fat (adjusted mean difference, -1.4% [95% CI, -2.2% to -0.7% ; $P<.001$ and -0.8% [95% CI, -1.6% to -0.07% ; $P=.03$) and visceral fat (adjusted mean difference, -3.9 cm^3 [95% CI, -6.0 to -1.7 cm^3 ; $P<.001$ and -2.8 cm^3 [95% CI, -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 (adjusted mean difference in peak $\dot{V}O_2$, 2.4 [95% CI, 0.4 - 4.5] mL/kg/min ; $P=.02$ and 2.4 [95% CI, 0.3 - 4.5] mL/kg/min ; $P=.03$, respectively). High- vs low-dose group effects were similar for these outcomes. There was no moderation by sex or race.

Conclusion In this trial, after 13 weeks, 20 or 40 min/d of aerobic training improved fitness and demonstrated dose-response benefits for insulin resistance and general and visceral adiposity in sedentary overweight or obese children, regardless of sex or race.

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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 race, aged 7 to 11 years, overweight or obese (≥ 85 th percentile body mass index [BMI]; calculated as weight in kilograms divided by height in meters squared),¹⁷ sedentary (no regular physical activity program >1 hour per week), no medical condition or medications that would affect study results or limit physical activity, and ability to provide a fasting blood sample at baseline. Informed consent and assent were obtained orally and in writing from parents or guardians and from children. 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 min/d of aerobic exercise), or a no-treatment control condition was performed by the statistician (J.L.W.), stratified by race and sex. As each cohort was enrolled, each participant was assigned a uniform (0, 1) random number using SAS software, versions 8.2 and 9.1 (SAS Institute Inc), within their respective race and sex group. If the number was between 0 and 0.33, the child was randomized to the low-dose group; between 0.34 and 0.67, to the high-dose group; and above 0.67, to the control group. Assignments were concealed until baseline testing was completed, then communicated to the study coordinator, who 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 exercise. The low- and high-dose exercise conditions were equivalent in intensity and differed only in duration and, therefore, volume (ie, energy expenditure) of daily exercise. Children assigned to the high-dose exercise condition were offered two 20-minute exercise bouts each school day. Children assigned to the low-dose exercise condition were included in the first 20-minute bout in the gymnasium and then went to another room for a 20-minute sedentary period.

The emphasis was on intensity, enjoyment, and safety, not competition or 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 (eg, Howe et al¹⁸). Points were awarded daily for an average heart rate higher than 150 beats/min in the program (S610i, Polar Electro; 30-second epoch) and redeemed for weekly prizes. The program handbook is available from the authors on request.

Outcomes

The prespecified primary outcomes of the study included insulin resistance (ie, insulin area under the curve [AUC]), fatness, visceral fat, and aerobic fitness; fasting glucose level 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 in-

cluded fasting insulin level, Matsuda index, disposition indexes, subcutaneous abdominal fat, and BMI *z* score.

Measurements

Measurements were conducted at baseline and repeated at posttest (after a mean 13 [SD, 1.6] weeks of intervention or control condition). Posttesting was scheduled 1 to 3 days following the child's last exercise session to minimize acute effects. Assessors were not blinded to these outcomes. Children were scheduled for the posttest in the order in which 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 (eg, 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 minutes prior to glucose ingestion (1.75 g/kg of dextrose based on ideal body weight, up to 75 g). Serum samples were taken every 30 minutes for 2 hours after glucose was consumed. Insulin AUC was calculated via the trapezoidal rule. Glucose was measured using the glucose oxidase method (Analox) and insulin using radioimmunoassay (human-specific insulin, Linco Research Inc). The mean intra-assay coefficients of variation for glucose and insulin assays are 0.61% and 4.5% and interassay coefficients of variation are 1.45% and 2.3%, respectively. Prediabetes status was determined by impaired fasting glucose (fasting serum glucose, 100–125 mg/dL) or impaired glucose tolerance (2-hour glucose, 140–199 mg/dL) at baseline.²⁰

Diabetes risk indexes that were either validated in children²¹ or demonstrated to predict the incidence of dia-

betes in adults²² were exploratory outcomes. The Matsuda index of insulin sensitivity was calculated.^{23,24} There is no clinically normal range for these indexes. Higher values on the Matsuda index indicate more insulin sensitivity, less insulin resistance, and less diabetes risk. At baseline, the Matsuda index range was 0.55 to 9.30; at posttest it was 0.75 to 7.20. 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 (ie, $\Delta\text{insulin}_{0-30}/\Delta\text{glucose}_{0-30}$).^{22,25} The disposition index based on fasting insulin (DI_{FI}) was the product of fasting insulin⁻¹ and the insulinogenic index.²¹ Higher values on the disposition indexes indicate better beta cell function (insulin secretion relative to insulin resistance) and lower diabetes risk. At baseline, the range for DI_{OGTT} was 0.22 to 19.35 and for DI_{FI} was 0.5 to 0.48. At posttest, the range for DI_{OGTT} was 0.22 to 19.01 and for DI_{FI} was 0.03 to 0.55. Twenty-nine individuals were excluded from the analyses for insulin AUC and Matsuda index and 6 from disposition indexes because of 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-assay and inter-assay coefficients of variation 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 for potential effects of pubertal development on insulin resistance.

Body Composition. Dual-energy x-ray absorptiometry (Hologic QDR-4500W) of the whole body was used to measure fatness. Abdominal visceral and subcutaneous fat content was measured with magnetic resonance imaging (1.5T; General Electric Medical Systems) of five 1-cm transverse slices around the L4-L5 disk.²⁶

Cardiovascular Fitness. Cardiovascular fitness was determined using a

multistage treadmill test modified from the protocol for poorly fit children (oxygen consumption [$\dot{V}O_2$] relative to body mass in milliliters per kilogram per minute; Sensormedics Vmax 229).^{27,28} The modified protocol incorporated a warm-up period of 2.5 mph, 0% slope for 2 minutes before the warm-up at 3 mph, 3% slope for 2 minutes in the original protocol. After the warm-up, the speed remained at 3 mph and slope increased by 2% every 2 minutes until the child decided to stop or until maximum oxygen consumption ($\dot{V}O_{2\text{max}}$) was reached. Because not all children attain $\dot{V}O_{2\text{max}}$, the peak $\dot{V}O_2$ value during the treadmill test was used as the primary fitness outcome.

Anthropometrics. Anthropometrics were measured at least twice until consistent measures were obtained. Body mass index percentiles and z scores were determined from body weight (in shorts and t-shirt; Detecto) and height (without shoes; HR100; Tanita).¹⁷ 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 (days per week) was determined by the question "On how many of the past 7 days did you participate in physical activity for at least 30 minutes 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 (days per week) 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 minutes 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 (kilocalories; Nutrition Data System for Research software; version 2006). Prior to recall, children and parents were trained in how

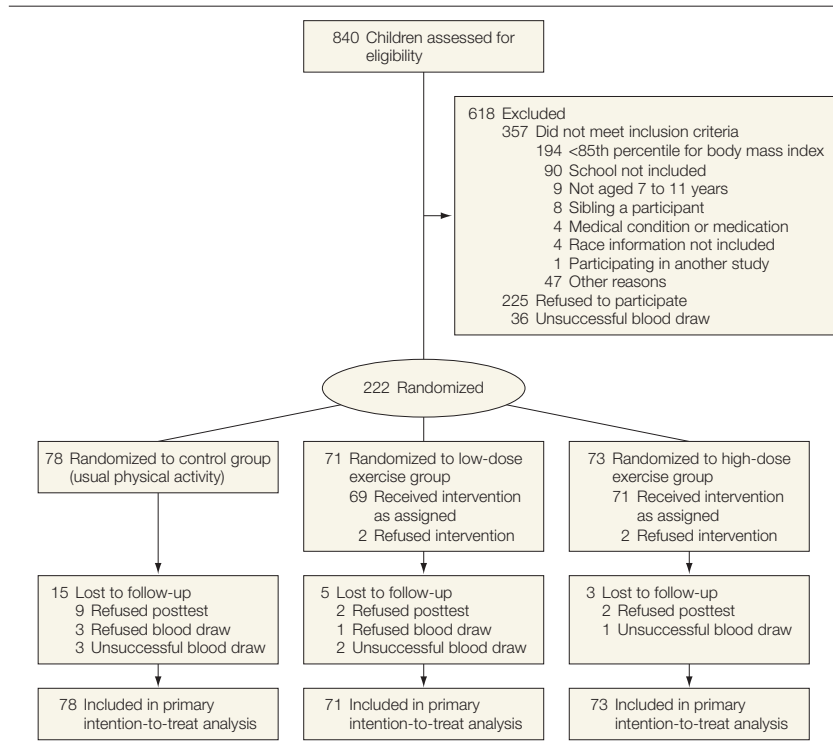
to maintain a diet record using food models, portion booklets, and containers for estimating serving size.

Energy Expenditure During Aerobic Training. Energy expenditure during the exercise sessions was estimated by first regressing $\dot{V}O_2$ on heart rate from each treadmill test. Participants' mean slope between baseline and posttest was used to adjust for improved fitness elicited by the intervention. Energy expenditure (kilocalories) and intensity (metabolic equivalents) in the exercise program were 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 energy expenditure from $\dot{V}O_2$.

Statistical Analyses

A planned sample size of 80 per group, allowing for 20% attrition resulting in 64 per group at posttest, was selected to provide 80% or more power using a 2-sided α level of .05 to detect group differences on most primary outcomes (insulin resistance and body fat, each 96%; visceral fat, 71%; and fitness, 98% power) based on results from prior studies that showed group differences in change in fasting insulin (-4.2 $\mu\text{U/mL}$), 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 software, version 9.2, and a 2-sided α level of .05 was set as significant. Data were examined for normality and logarithmic transformations applied if necessary. Group differences at baseline were determined using analysis of variance and χ^2 tests.

Repeated-measures mixed models were used with maximum likelihood estimation and a Kenward-Rogers adjustment to the degrees of freedom in an intention-to-treat analysis of each outcome measure using all available data. Base models for each outcome measure included the fixed effects of group and measurement period (baseline or posttest) and their interaction,

Figure 1. Participant Flow

and controlled cohort, race, and sex. Participant nested within group was considered a random effect. The modeled covariance structure between measurement periods was unstructured because there were only 2 measurement periods. Other potential covariates included Tanner stages, sex hormone levels, and family history of diabetes at baseline. If either Tanner stage variable was significant, both were included. Prespecified moderators (sex, race, and sex \times 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 3 groups of the change from baseline to posttest tested dose-response effects of exercise intervention. Pairwise comparisons of

change between groups were performed.

RESULTS

Participant flow is presented in **FIGURE 1**. We randomized 222 children to the control ($n=78$), low-dose exercise ($n=71$), or high-dose exercise ($n=73$) condition. Similar baseline characteristics were observed in the 3 groups (**TABLE 1**). A majority of children (85%) were obese and 28% had prediabetes.

The numbers of minor adverse events that occurred during testing were similar between groups (5, 7, and 6 in control, low-dose, and high-dose groups, respectively; $P=.85$), as was the duration between baseline and posttest (mean, 129 [SD, 19], 129 [SD, 15], and 128 [SD, 13] days, respectively; $P=.91$). Duration of intervention, number of minor adverse events during intervention, attendance, heart rate, and intensity were similar in the low- and high-dose exercise groups (**TABLE 2**). There was 1 serious adverse event (foot fracture in the low-dose exercise group). As expected,

daily and total energy expenditure were higher in the high-dose vs the low-dose exercise 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 stage for insulin AUC, Matsuda index, fasting insulin and glucose, and sex hormones for body fat.

Primary Outcomes: Insulin Resistance, Fatness, and Fitness

Changes in outcomes by exercise dose are shown in **FIGURE 2**, **FIGURE 3**, and **TABLE 3**. Significant downward linear dose-response trends, with larger reductions between baseline and posttest for the high-dose exercise group than for the control group, were observed for insulin AUC (adjusted mean difference, $-3.56 \times 10^3 \mu\text{U/mL}$; 95% CI, -6.26 to $-0.85 \times 10^3 \mu\text{U/mL}$; $P=.01$), body fat (adjusted mean difference, -1.4% ; 95% CI, -2.2% to -0.7% ; $P<.001$), and visceral fat (adjusted mean difference, -3.9 cm^3 ; 95% CI, -6.0 to -1.7 cm^3 ; $P<.001$). Reductions in the low-dose exercise group, which were larger than changes in the control group, were also observed for insulin AUC (adjusted mean difference, $-2.96 \times 10^3 \mu\text{U/mL}$; 95% CI, -5.69 to $-0.22 \times 10^3 \mu\text{U/mL}$; $P=.03$), body fat (adjusted mean difference, -0.8% ; 95% CI, -1.6% to -0.07% ; $P=.03$), and visceral fat (adjusted mean difference, -2.8 cm^3 ; 95% CI, -4.9 to -0.6 cm^3 ; $P=.01$). Although adjusted mean differences in change were larger in the high-dose vs low-dose exercise group for these outcomes, the difference in change between the exercise groups was not significant. Very similar increases for both exercise groups were observed for fitness, with each group's change significantly larger than that of the control condition (adjusted mean difference in peak $\dot{V}\text{O}_2$, 2.4 mL/kg/min ; 95% CI, 0.4 – 4.5 mL/kg/min ; $P=.02$ in the high-dose exercise group and 2.4 mL/kg/min ; 95% CI, 0.3 – 4.5 mL/kg/min ; $P=.02$ in the low-dose exercise group vs the control group), with no significant difference between exercise doses.

Other Outcomes

No significant effect of exercise was detected for the secondary outcome of fasting glucose level. Dose-response benefits of exercise were indicated by

significant downward trends across groups for fasting insulin level (adjusted mean difference, $-3.98 \mu\text{U/mL}$; 95% CI, -7.04 to $-0.91 \mu\text{U/mL}$; $P=.01$ for high-dose exercise and

mL ; 95% CI, -6.67 to $-0.43 \mu\text{U/mL}$; $P=.03$ for low-dose exercise vs control), and subcutaneous abdominal fat (adjusted mean difference, -24 cm^3 ; 95% CI, -32 to -15 cm^3 ; $P<.001$ for

Table 1. Baseline Participant Characteristics^a

Characteristics	Total (N = 222)	Control (n = 78)	Low-Dose Exercise (n = 71)	High-Dose Exercise (n = 73)
Age, y	9.4 (1.1)	9.4 (1.1)	9.3 (0.9)	9.4 (1.2)
Male, No. (%)	94 (42)	30 (38)	31 (44)	33 (45)
Black, No. (%)	129 (58)	43 (55)	42 (59)	44 (60)
Hispanic, No. (%)	6 (3)	0	3 (4)	3 (4)
Family history of diabetes, No. (%)	134 (60)	49 (63)	41 (58)	44 (60)
Body mass index ^b	25.9 (4.4)	26.3 (4.6)	25.9 (4.1)	25.6 (4.5)
z score	2.1 (0.4)	2.1 (0.4)	2.1 (0.4)	2.0 (0.4)
Percentile	97 (3.0)	97 (3.2)	97 (2.8)	97 (3.0)
Obesity, No. (%)	188 (85)	67 (86)	60 (85)	61 (84)
Severe obesity, No. (%)	70 (32)	24 (31)	28 (39)	18 (25)
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)
Subcutaneous fat, cm^3	275 (109)	282 (116)	275 (104)	267 (107)
Peak $\dot{V}\text{O}_2$, mL/kg/min	27.6 (5.5)	26.8 (4.8)	27.8 (5.5)	28.5 (6.0)
Prediabetes, No. (%)	63 (28)	20 (26)	19 (27)	24 (33)
Tanner stage, No. (%) ^c				
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
V	1 (<1)	0	1 (1)	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
Estradiol in girls, pg/mL	5.4 (9.1)	5.7 (6.8)	6.0 (13.7)	4.5 (4.9)
Testosterone in boys, ng/dL	18 (25)	22 (35)	17 (25)	16 (10)
Insulin AUC, $\times 10^3 \mu\text{U/mL}$	16.3 (10.7)	16.3 (9.7)	16.1 (9.5)	16.4 (12.8)
Fasting glucose level, mg/dL	92.9 (7.8)	93.4 (8.3)	91.9 (6.3)	93.4 (8.5)
Fasting insulin level, $\mu\text{U/mL}$	21.9 (12.4)	23.1 (14.2)	21.5 (11.1)	21.1 (11.5)
Matsuda index ^d	2.4 (1.4)	2.5 (1.7)	2.2 (1.0)	2.4 (1.3)
DI_{OGTT} ^e	5.6 (3.3)	5.5 (3.3)	5.8 (3.6)	5.4 (3.1)
DI_{FI} ^e	0.14 (0.09)	0.14 (0.09)	0.14 (0.09)	0.14 (0.08)
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; DI_{FI} , disposition index based on fasting estimate of insulin sensitivity ($1/\text{fasting insulin} \times \text{insulinogenic index}$); DI_{OGTT} , disposition index based on oral glucose tolerance test measurement of insulin sensitivity (Matsuda index \times insulinogenic index); $\dot{V}\text{O}_2$, oxygen consumption.

SI conversion factors: To convert glucose to mmol/L , multiply by 0.0555; to convert insulin to pmol/L , multiply by 6.945; to convert energy intake to J, multiply by 4186.8; to convert estradiol to pmol/L , multiply by 3.671; to convert testosterone to nmol/L , multiply by 0.0347.

^aData are expressed as mean (SD) unless otherwise noted. There were no significant group differences ($P>.05$).

^bBody mass index is calculated as weight in kilograms divided by height in meters squared. Obesity indicates a body mass index ≥ 95 th percentile. Severe obesity indicates a body mass index ≥ 99 th percentile.

^cPercentages may not total 100 because of rounding.

^dThe Matsuda index has no normal range. Higher values indicate more insulin sensitivity and less diabetes risk. At baseline, the range was 0.55 to 9.30.

^eThe disposition indexes have no normal range. Higher values indicate better beta cell function and lower diabetes risk. At baseline, the range for DI_{OGTT} was 0.22 to 19.35 and the range for DI_{FI} was 0.05 to 0.48. At posttest, the range for DI_{OGTT} was 0.22 to 19.01 and the range for DI_{FI} was 0.03 to 0.55.

high-dose exercise and -15 cm^3 ; 95% CI, -24 to -7 cm^3 ; $P < .001$ for low-dose exercise vs control). For BMI z score, there was a significant downward trend, and differences in change were observed for the high-dose exercise group vs the other groups (adjusted mean difference, -0.1 ; 95% CI, -0.14 to -0.05 ; $P < .001$ vs control and -0.05 ; 95% CI, -0.10 to -0.01 ; $P = .02$

vs low-dose exercise), but there was no difference in effect between the low-dose exercise and control groups.

A significant upward trend with exercise dose was seen on the Matsuda index (adjusted mean difference, 0.67 ; 95% CI, 0.26 - 1.08 ; $P = .002$ for high-dose exercise and 0.56 ; 95% CI, 0.14 - 0.97 ; $P = .009$ for low-dose exercise vs control). An upward trend and differ-

ence in change between the high-dose exercise and control groups was shown for DI_{OGTT} (adjusted mean difference, 0.84 ; 95% CI, 0.02 - 1.65 ; $P = .04$), but the change in the low-dose exercise group was similar to those in the high-dose exercise and control groups. No group difference in change was detected for DI_{FI} .

For fasting insulin level, a significant interaction of family history of diabetes \times group \times time was found. However, excluding an extreme fasting insulin value at posttest ($136 \text{ } \mu\text{U/mL}$) without excluding other data for that child (a control group participant with no family history of diabetes) eliminated the interaction (Table 3). There were no other significant interactions of group \times time with family history, race, sex, or prediabetes status.

Table 2. Measurements Obtained During the Intervention Period^a

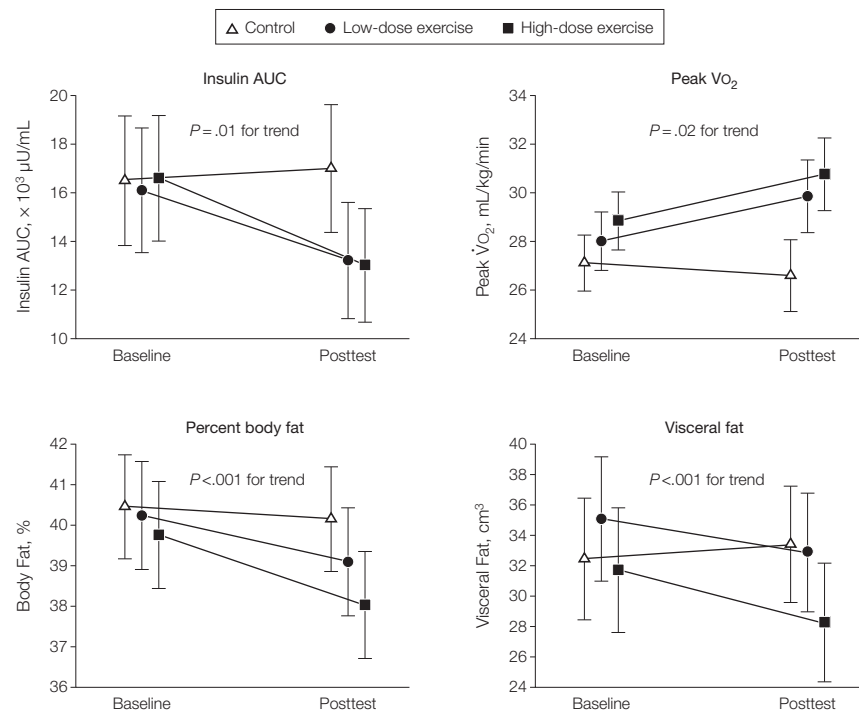
	Low-Dose Exercise	High-Dose Exercise	P Value
Minor adverse events, No.	31	35	.62
Duration of intervention, wk	13 (1.5)	13 (1.7)	.93
Attendance, %	85 (12)	84 (14)	.88
Daily average heart rate, beats/min	166 (7)	165 (9)	.37
Intensity, metabolic equivalents ^b	7.5 (1.4)	7.5 (1.4)	.94
Daily energy expenditure, kcal/d ^b	134 (24)	269 (70)	<.001
Total energy expenditure, kcal ^b	6727 (1719)	13025 (4144)	<.001

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

^aData are expressed as mean (SD) unless otherwise noted.

^bIntensity and energy expenditure were estimated from daily attendance and heart rate measures using the mean slope of oxygen consumption regressed on heart rate from each child's treadmill tests at baseline and posttest.

Figure 2. Intention-to-Treat Mixed-Model Repeated-Measures Analysis of Variance of the Effect of Group on Primary Outcomes



The P value in each panel indicates the test of the dose-response trend; ie, whether change between baseline and posttest differed between the control and high-dose exercise (40-min/d) groups. Error bars indicate 95% confidence intervals. AUC indicates area under the curve; VO_2 , oxygen consumption.

COMMENT

This randomized clinical trial in sedentary overweight and obese children, 28% of whom had prediabetes, quantified the efficacy of monitored aerobic exercise training to reduce diabetes risk (ie, insulin resistance) and other indexes of cardiometabolic risk. The trial had exceptional adherence and retention. A daily aerobic exercise intervention with a duration of 13 weeks and no dietary restrictions showed dose-response benefits as assessed by insulin response to OGTT and fasting insulin. The high-dose exercise intervention demonstrated significant benefit on DI_{OGTT} , a surrogate index of diabetes risk integrating insulin resistance and beta cell function and an excellent predictor of diabetes incidence in adults.^{22,33} The reductions in fasting insulin recategorized most participants in the exercise groups from high to borderline high clinical status 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 2 exercise doses showed similar improvements in fitness. No evidence for energy expenditure compensation was found.

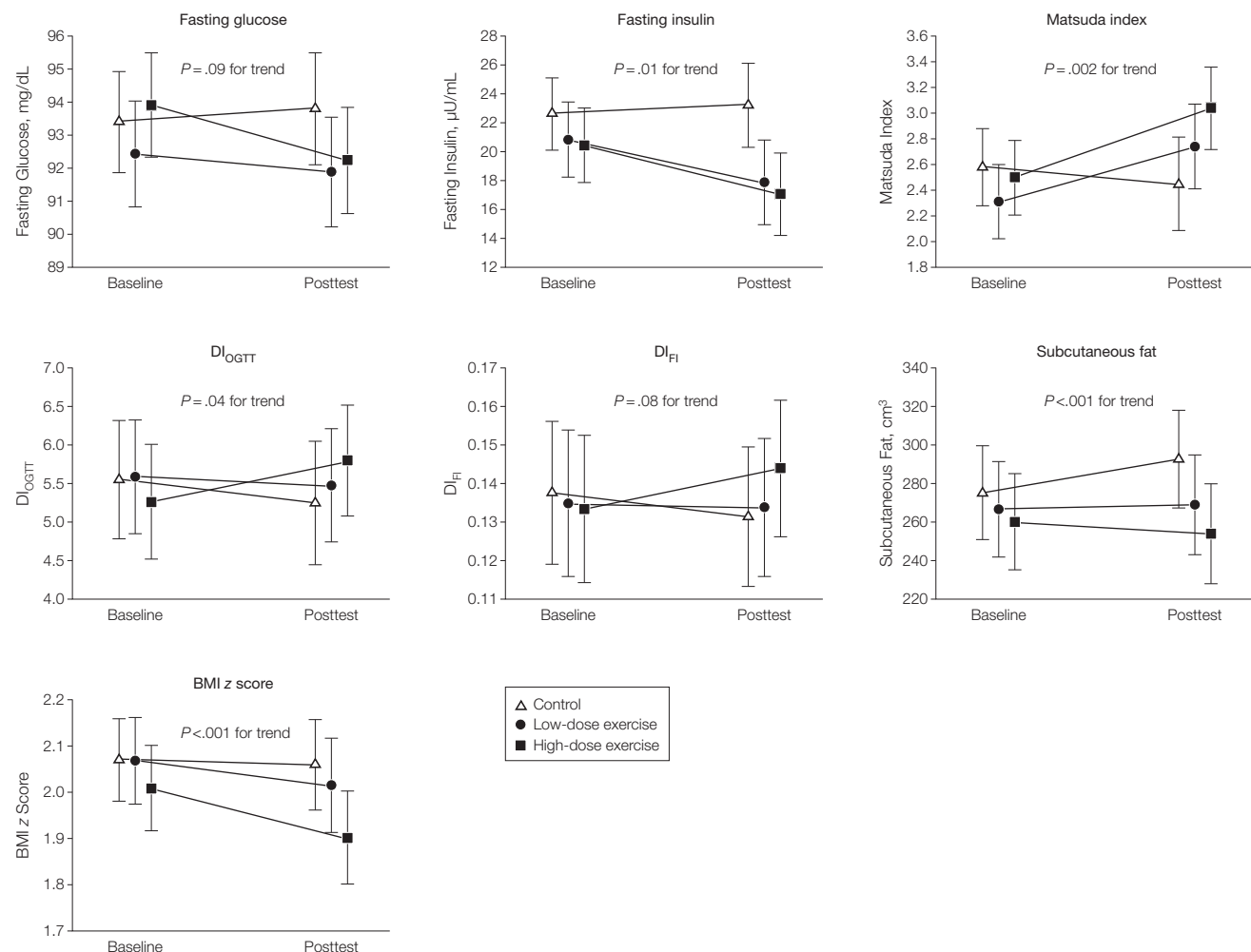
No difference in efficacy was observed between boys and girls, black and white children, or children with prediabetes vs normoglycemic children. These consistent effects of intervention do not conflict with cross-sectional race differences reported in the literature (lower visceral adiposity, greater insulin resistance, and higher disposition index in black children)³⁵⁻³⁷ but contrast with the prospective finding that black girls were less sensitive than white girls to the effects of physical activity on fat accretion.³⁸ An ef-

fect modification for the effect of exercise on fasting insulin was detected for family history, but this appeared to be due to 1 extreme value, probably caused by nonadherence to 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 exercise conditions was larger than the additional benefit observed between the low- and

high-dose exercise groups. Greater benefit has been 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 exercise groups showed similar effects on insulin resistance. A similar result for insulin resistance was obtained by the STRRIDE study, where the low-volume exercise group had similar improvements as the high-volume exercise group at the same intensity. Moderate as well as vigorous activity

Figure 3. Intention-to-Treat Mixed-Model Repeated-Measures Analysis of Variance of the Effect of Group on Secondary and Exploratory Outcomes



The P value in each panel indicates the test of the dose-response trend; ie, whether change between baseline and posttest differed between the control and high-dose (40-min/d) exercise groups. Error bars indicate 95% confidence intervals. DI_{OGTT} indicates disposition index based on oral glucose tolerance test measurement of insulin sensitivity (Matsuda index × insulinogenic index); DI_{FI}, disposition index based on fasting estimate of insulin sensitivity (1/fasting insulin × insulinogenic index); BMI, body mass index.

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 The low- and high-dose exercise interventions showed nearly identical effects on fitness. 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 minutes vs 20 minutes of daily vigorous activity.

Although several exercise studies have now used an 8- to 9-month training period, more than twice that of the current study, the 5-d/wk frequency in this study is rare.⁴³ The Cochrane review of obesity treatment trials⁴⁴ includes only 9 focused on physical ac-

tivity in children younger than 12 years 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 participants from once a month to 3 times a week) and few studies isolated exercise, instead combining it with a dietary intervention.

Large, well-conducted school-based studies have tested effects of physical activity on obesity in children and have failed to reduce obesity, perhaps because of inadequate dose^{45,46}; 1 study succeeded only in girls.⁴⁷ The HEALTHY study was designed to reduce risk of 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 3 times the effect on BMI *z* score and 8 times 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 months) 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.

The relatively short duration of the intervention and lack of follow-up assessment of possible lasting effects are limitations of the current study. In addition, participants were not blinded to condition because it was a behavioral intervention; measurement staff were not blinded; the control group was not

Table 3. Changes in Diabetes Risk, Fitness, and Fatness Outcomes^a

Outcomes	Adjusted Mean Difference, Low-Dose vs Control (95% CI)	P Value, Low-Dose vs Control	Adjusted Mean Difference, High-Dose vs Low-Dose (95% CI)	P Value, High-Dose vs Low-Dose	Adjusted Mean Difference, High-Dose vs Control (95% CI)	P Value for Trend, High-Dose vs Control ^b
Primary outcomes						
Insulin AUC, $\times 10^3$ μ U/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
Peak $\dot{V}O_2$, 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
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 level, 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 level, μ U/mL						
All data ^c	-3.55 (-6.67 to -0.43)	.03	-0.43 (-3.46 to 2.60)	.78	-3.98 (-7.04 to -0.91)	.01
Extreme value excluded ^c	-2.61 (-5.58 to 0.36)	.08	-0.45 (-3.35 to 2.46)	.76	-3.05 (-5.98 to -0.13)	.04
No family history of diabetes ^{c,e}	-7.39 (-12.22 to -2.56)	.003	-2.46 (-7.15 to 2.22)	.30	-9.85 (-14.72 to -4.98)	<.001
Family history of diabetes ^{c,e}	-1.4 (-5.28 to 2.49)	.48	0.91 (-2.87 to 4.69)	.64	-0.49 (-4.24 to 3.26)	.80
Matsuda index ^{c,f}	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} ^g	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 _F ^g	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
Body mass index <i>z</i> score	-0.04 (-0.09 to 0.00)	.06	-0.05 (-0.10 to -0.01)	.02	-0.10 (-0.14 to -0.05)	<.001

Abbreviations: AUC, area under the curve; DI_F, disposition index based on fasting estimate of insulin sensitivity (1/fasting insulin \times insulinogenic index); DI_{OGTT}, disposition index based on oral glucose tolerance test measurement of insulin sensitivity (Matsuda index \times insulinogenic index); $\dot{V}O_2$, oxygen consumption.

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

^aDifferences between groups in change from baseline to posttest adjusted for cohort, sex, and race.

^bTest of linear trend is equivalent to test of high-dose exercise group vs control group.

^cAdditionally adjusted for Tanner stages.

^dAdditionally adjusted for sex hormone level.

^eStratified because of interaction with family history of diabetes, which was eliminated by excluding 1 extreme value at posttest in the control group for a child with no family history.

^fThe Matsuda index has no normal range. Higher values indicate more insulin sensitivity and less diabetes risk. At baseline, the range was 0.55 to 9.30 and at posttest was 0.75 to 7.20.

^gThe disposition indexes have no normal range. Higher values indicate better beta cell function and lower diabetes risk. At baseline, the range for DI_{OGTT} was 0.22 to 19.35 and the range for DI_F was 0.05 to 0.48. At posttest, the range for DI_{OGTT} was 0.22 to 19.01 and the range for DI_F was 0.03 to 0.55.

offered an attention-control intervention program; and the daily snack offered only to the exercise groups may have affected outcomes.

Twenty minutes of aerobic exercise per school day for just a few months showed benefits vs 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 provided during the school day in 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 this exercise intervention on cognition and mathematics achievement, which may increase its appeal to educators.⁵³ Elements of the program that may have contributed to its success were limiting enrollment to overweight and obese children; use of inclusive, appealing interventions with fun, simple games that minimized barriers to participation; use of heart rate as a physiological index of effort; and provision of contingent rewards for effort rather than athletic performance to encourage even unfit children to exercise intensely.

In conclusion, in this randomized controlled trial, 13 weeks of 20- or 40-min/d aerobic training resulted in improvement in diabetes risk as estimated by insulin resistance, fitness, and general and visceral adiposity in sedentary overweight or obese children regardless of race or sex, with a dose-response gradient for insulin resistance and adiposity.

Author Contributions: Dr Davis 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.

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Analysis and interpretation of data: Davis, Pollock, Waller, Allison, Dennis, Bassali, Meléndez, Gower.

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Statistical analysis: Davis, Pollock, Waller.

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