Effects of Exercise Modality on Insulin Resistance and Ectopic Fat in Adolescents with Overweight and Obesity: A Randomized Clinical Trial

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Objective To examine whether a combined aerobic exercise and resistance exercise is more effective than either aerobic exercise or resistance exercise alone in improving insulin sensitivity and reducing total adiposity and ectopic fat in adolescents.

Study design A total of 118 sedentary adolescents with overweight/obesity (body mass index >85th percentile, 12-17 years) were recruited from October 2013 through April 2017 at Children's Hospital of Pittsburgh. Participants were randomized to 1 of the following 6-month exercise groups (3 d/wk, 180 min/wk): aerobic exercise (n = 38), resistance exercise (n = 40), and combined aerobic exercise and resistance exercise (n = 40). The primary outcome was the change in insulin-stimulated glucose disposal by a 3-hour hyperinsulinemic-euglycemic clamp. The secondary outcomes were changes in liver fat by proton magnetic resonance spectroscopy and intermuscular adipose tissue by computed tomography.

Results Of the 118 participants randomized, 85 participants (72%) completed the study with 90% exercise attendance. Total adiposity reduced similarly in all groups (–2%, $P < .05$). After adjusting for age and sex, insulin-stimulated glucose disposal increased ($P < .05$) in all groups, with the increase in the aerobic exercise group being greater than the resistance exercise group (1.7 ± 0.1 vs 0.7 ± 0.1 mg/kg/min, $P < .05$) but not different from the combined group (1.2 ± 0.1 mg/kg/min). Liver fat was reduced ($P < .05$) in the aerobic exercise (–0.6%) and combined (–0.6%) groups but not in the resistance exercise group (–0.3%, $P > .05$). Intermuscular adipose tissue decreased ($P < .05$) similarly in all groups.

Conclusion Combined aerobic exercise and resistance exercise and aerobic exercise alone are similarly beneficial in improving insulin sensitivity and reducing ectopic fat in adolescents with obesity. *(J Pediatr 2019;206:91-8).*

Trial registration ClinicalTrials.gov: NCT01938950.

Recent national data indicate that 1 in 3 children and adolescents in the US are either overweight or obese.[1] In parallel with the increasing prevalence of childhood obesity, the prevalence of prediabetes,[2] type 2 diabetes mellitus (T2DM),[3] and nonalcoholic fatty liver disease[4] also are increasing in youth. Given that physical activity level decreases substantially between childhood and adolescence[5] and that physically active youth are more likely to remain active in adulthood,[6] the enhancement of physical activity during adolescence is of importance.

The 2008 Physical Activity Guidelines for Americans[7] recommend that children and adolescents should do 60 minutes or more of physical activity per day. The guidelines suggest that the activity should include both moderate- or vigorous-intensity physical activity at least 3 days a week and muscle-strengthening physical activity at least 3 days a week to obtain health benefits.[7] Further, adult studies have shown that the combination of aerobic exercise and resistance exercise is a better strategy than either aerobic exercise or resistance exercise alone for improving glycemic control and insulin sensitivity.[8-10] However, it is important to note that the exercise dose in terms of exercise duration in these interventions[8,10] was not matched between the exercise groups and the combined aerobic exercise and resistance exercise group generally exercised for a significantly longer time than the resistance exercise– or aerobic

1-RM	One-repetition maximum
BMI	Body mass index
CHP	Children's Hospital of Pittsburgh
EE	Energy expenditure
FFM	Fat free mass
IMAT	Intermuscular adipose tissue
MRS	Magnetic resonance spectroscopy
OGTT	Oral glucose tolerance test
R_d	Insulin-stimulated glucose disposal
T2DM	Type 2 diabetes mellitus
VO_2	Maximum rate of oxygen consumption

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Funded by the National Heart, Lung, and Blood Institute (R01HL114857 [to S.L.]), and the National Institutes of Health Clinical and Translational Science Award (UL1 RR024153 and UL1TR000005) to the Pediatric Clinical and Translational Research Center. The authors declare no conflicts of interest.

https://doi.org10.1016/j.jpeds.2018.10.059

exercise–only groups. In adults with T2DM, Church et al reported that when similar exercise duration was maintained, only the combined exercise, but not either exercise modality alone, was associated with significant reduction in glycated hemoglobin A1c level.[9]

Previously, we and others reported significant reductions in liver fat following 3 months of aerobic exercise[11-13] or resistance exercise[12] in adolescents with obesity. We also demonstrated that in girls with obesity, both 3 months of aerobic exercise and resistance exercise resulted in significant reductions in intermuscular adipose tissue (IMAT),[13] a strong correlate of insulin resistance in adolescents.[14] To our knowledge, the independent and combined effects of aerobic exercise and resistance exercise on liver fat and IMAT have not been examined in adolescents.

Currently, whether a combination of aerobic exercise and resistance exercise is a better exercise strategy as compared with a similar duration of either aerobic exercise or resistance exercise alone for reducing total adiposity and ectopic fat in the liver and skeletal muscle and improving insulin sensitivity is unknown in youth. Therefore, we conducted a randomized trial to examine whether a combined aerobic and resistance exercise is more effective than either aerobic or resistance exercise alone in improving insulin sensitivity and reducing total % body fat, fatty liver, and skeletal muscle lipid in previously sedentary adolescents with overweight and obesity.

Methods

We conducted a 6-month, single-center, randomized trial (ClinicalTrials.gov: NCT01938950) with a parallel group design. Participants were recruited from November 2013 through April 2017 at Children's Hospital of Pittsburgh (CHP) of the University of Pittsburgh Medical Center. The final follow-up evaluation was on June 21, 2017. Adolescents with overweight and obesity (body mass index [BMI] >85th percentile and <40 kg/m^2) were recruited via flyers posted in public transportation venues, the university campus and hospitals, and from the Weight Management and Wellness Center at CHP. Parental informed consent and child assent were obtained from all participants before participation. Inclusion criteria included that the subjects be 12-17 years of age, pubertal (Tanner stages II-V), nonsmokers, and physically inactive (no participation in structured physical activity for past 3 months before study entry except school physical education classes). Exclusion criteria included participation in structured exercise, significant weight change (Δ BMI>2-3 kg/m^2) in the past 3 months before study entry, endocrine disorders (eg, polycystic ovary syndrome, diabetes), syndromic obesity, psychiatric disorders, or the use of chronic medications that influence glucose metabolism (ie, insulin sensitizers) or body composition.

Pubertal development was assessed according to Tanner criteria[15] by a certified nurse practitioner. All participants underwent a complete physical examination and routine hematologic and biochemical tests at the Pediatric Clinical and Translational Research Center at CHP. Baseline and postintervention evaluations were completed during an overnight inpatient admission at CHP. The investigation was approved by the University of Pittsburgh institutional review board (PRO12080401).

Randomization

Participants were assigned randomly to 1 of 3 exercise training groups for 24 weeks: aerobic exercise (aerobic exercise, n = 38), resistance exercise (resistance exercise, n = 40), or combined aerobic exercise and resistance exercise (n = 40) group (**Figure 1**; available at www.jpeds.com). A block randomization was done based on sex and age (12-15 years, 15-17 years), which was performed by the study biostatistician. Randomization was performed after completing all baseline evaluations. Participants and exercise trainers could not be blinded to group assignment after randomization because of the nature of the intervention. However, the main study outcome (insulin sensitivity) and the secondary study outcomes (liver fat and IMAT) were measured and analyzed by staff and investigators who were blinded to group assignment.

Dietary Intervention

Before baseline evaluations, participants attended two 1-hour individual nutrition counseling sessions on proper food selection with the study dietitian. During this dietary run-in period (2-4 weeks), participants were asked to follow a healthy weight maintenance calorie intake (55%-60% carbohydrate, 15%-20% protein, and 20%-25% fat), which was determined using the Harris–Benedict equation.[16] During the 6-month exercise intervention period, participants were asked to follow the calorie intake targets determined at baseline to ensure that the negative energy balance was induced by regular exercise alone and not from dieting. Adherence to dietary regimen was monitored by examination of body weight before each exercise session and a monthly 24-hour dietary recall was performed by the study dietitian using a computerized program (Food Processor; Esha Research, Salem, Oregon).

Exercise Intervention

Exercise sessions took place at 2 locations in Pittsburgh: the downtown Pittsburgh PNC-YMCA and the CHP exercise laboratory. All exercise sessions were by appointment and were supervised by an exercise physiologist or exercise science students. All participants were asked to attend exercise sessions, 3 times/wk, 60 min/session, for 6 months. Exercise training sessions were delivered in small group settings (1-2 participants: 1 trainer ratio) to ensure participant's safety and compliance. Missed exercise sesssions due to sickness and vacations were recheduled by appointment. Detailed exercise regimens are described in **Table I** (available at www.jpeds.com). Participants in the aerobic exercise and combined groups wore a heart rate monitor (Polar Oy, Kempele, Finland) during aerobic exercise sessions to ensure achievement of the target heart rate (50%-65% of peak maximum rate of oxygen consumption [VO_2]). Energy expenditure (EE) was estimated using the heart rate–VO_2 relationship obtained from the maximal graded treadmill test. The heart rates were translated into estimated EE using the assumption that 1 L of O_2 equals 5 kcal of EE.[17] The relationship between the heart rate and VO_2 was re-evaluated during the subsequent maximal treadmill tests at week 4 and week 12 to reassess the heart rate–EE relationship.

Total Fat and Anthropometric Measurements

Total fat and fat free mass (FFM) was assessed by dual-energy X-ray absorptiometry using lunar iDXA (GE Healthcare, Madison, Wisconsin).[18] Body weight was measured with the patient in a hospital gown to the nearest 0.1 kg using a distal scale, and height was measured to the nearest 0.1 cm using a fixed wall stadiometer. With the patient in a standing position, waist circumference was measured at the superior edge of the iliac crest and the average of 2 measures was used in the analyses.

Two-Hour Oral Glucose Tolerance Test (OGTT)

Participants reported to the Pediatric Clinical and Translational Research Center after an overnight fast (minimum 10 hours) for a 2-hour OGTT (1.75 g/kg, max 75 g) to assess for glucose tolerance status.[19] Arterialized heated-hand venous blood samples were obtained at −15, 0, 15, 30, 60, 90, and 120 minutes for determination of plasma glucose with a glucose analyzer (YSI, Inc, Yellow Springs, Ohio).

Following the OGTT, participants were admitted and stayed overnight in the hospital for the hyperinsulinemic-euglycemic clamp the next morning. Participants were fed a standardized lunch and dinner and fasted overnight. One participant in the combined group did not undergo OGTT test at 6 months due to scheduling issues.

Whole-Body Insulin-Stimulated Glucose Disposal (R_d) by the Hyperinsulinemic-Euglycemic Clamp

Insulin sensitivity was measured as the rate of peripheral R_d during the 3-hour 80 mU/m^2/min hyperinsulinemic–euglycemic clamp performed from 09:30 a.m. to 12:30 p.m. as reported by us previously.[20] To summarize, intravenous crystalline insulin (Humulin; Lilly, Indianapolis, Indiana) was infused at a constant rate of 80 mU/m^2 per min, and plasma glucose was clamped at 5.6 mmol/L with a variable-rate infusion of 20% dextrose based on arterialized plasma glucose determinations using a glucose analyzer (YSI, Inc, Yellow Springs, Ohio) every 5 minutes. R_d was calculated by using the average exogenous glucose infusion rate during the last 30 minutes of steady state. The clamp experiment was performed by a certified nurse practitioner under the direction of pediatric endocrinologists. Postexercise intervention evaluations and clamp test were performed at least 48-72 hours after the last exercise session to control for the well-known effects of acute exercise on glucose uptake.[21] Among 118 randomized participants, 2 subjects' (1 resistance exercise, 1 combined) clamp test at baseline could not be completed due to difficulty with intravenous access. One participant in the combined group did not undergo clamp test at 6 months, as she refused to stay overnight at CHP.

Liver Fat Content by Proton Magnetic Resonance Spectroscopy (^{1}H-MRS)

^{1}H-MRS was performed with a 3.0-Tesla magnetic resonance system (Tim Trio; Siemens, Erlangen, Germany) using a body matrix coil and a spine matrix (Siemens) as shown by us previously.[12,13] A total of 8 spectra (repetition time = 4000 milliseconds, echo time = 30 milliseconds) were obtained in a measuring time of 32 seconds without water suppression and averaged for the determination of intracellular water and lipid content. The AMARES algorithm in the Java-based magnetic resonance user interface (jMRUI) software package[22] was used to quantify the area under the curve of the methylene peak of lipid at 1.3 ppm and the water peak at 4.7 ppm. At baseline, 4 subjects (2 aerobic exercise, 2 combined) could not complete ^{1}H-MRS due to claustrophobia. One subject in the resistance exercise group was excluded in the liver fat data analyses, as this subject had 27.8% of liver fat (9 SDs above the mean). Excluding this subject did not alter the significance of our results.

Skeletal Muscle Composition

Computed tomography imaging was obtained on a GE Scanner (GE Medical Systems, Milwaukee, Wisconsin) using 170 mA, 120 kV, a 512 × 512 matrix, and 48-cm field of view as shown by us previously.[14] Using an external landmark, 1 axial image was obtained at the mid-point between the inguinal crease and superior edge of the patella. IMAT area was defined as adipose tissue area beneath the fascia lata surrounding skeletal muscle and adipose tissue area between muscle bundles.[23] Mean muscle attenuation, a measure of muscle density, was measured as the mean attenuation value for all pixels within the range of 0-150 HU using commercially available software (Slice-O-Matic, Tomovision Inc, Montreal, Quebec, Canada).

Cardiorespiratory Fitness and Muscular Strength

Cardiorespiratory fitness was determined using a maximal graded treadmill test with the use of standard open-circuit spirometry techniques (True One 2400; Parvo Medics, Sandy, Utah) until volitional fatigue as shown previously.[12,13] For the initial 2 minutes, the grade was set at 0%, after which time it was increased to 2% for the third minute and increased by 1% increments every minute thereafter. Muscular strength was assessed with a one-repetition maximum (1-RM) test for the chest press and leg press using weight stack equipment (Precor, Woodinville, Washington).[12,13] Muscular strength index was calculated as the sum of the 1-RM scores for the chest and leg press expressed per kg of body weight.[24] For postintervention evaluations, 2 subjects refused to undergo peak VO_2 and 1-RM tests, and 1 subject could not perform these tests due to muscle pain.

Changes in Study Protocol

We terminated the study early on June 30, 2017, because the principal investigator relocated to Korea. We shortened the length of exercise interventions from 24 weeks to 20 weeks-22 weeks for 4 participants to complete their postintervention evaluations in June 2017 before study termination. Three participants who completed the baseline evaluations could not have postintervention evaluations because of the early termination of the trial, which was approved by the institutional review board.

Statistical Analyses

The primary outcome of this study was the change in whole-body R_d measured by a 3-hour hyperinsulinemic-euglycemic clamp. The power calculations were based on our previous studies[12,13] to provide a statistical power of 80% to detect a difference in R_d of 0.71 mg/kg/min (SD: 1.1 mg/kg/min) between 2 exercise groups at 6 months.

A one-way ANOVA and Fisher exact test were performed to examine group differences at baseline. When the ANOVA *P* value was <.05, a Tukey post hoc comparison test was used for group differences. All randomized subjects were included in the analysis, and the effect of treatment was evaluated by intent-to-treat analysis. The missing data in the 6-month outcomes were imputed using the conditional mean method based on the treatment status, baseline age, and sex. Pairwise comparisons of changes in primary and secondary outcome values among groups were conducted using a general linear regression model adjusting for baseline age and sex. The adjusted means and SEs were calculated using the same model for each exercise group. Paired *t* tests were performed to compare the pre- and postvalues within each exercise group. Relationships between changes in glucose disposal and total and ectopic fat were determined using Pearson correlation coefficients. Statistical procedures were conducted in R, version 3.4.1[25] and SPSS (version 24; IBM Corp, Armonk, New York).

Results

Of the 118 participants randomized, 85 participants (30 aerobic exercise, 28 resistance exercise, and 27 combined) completed the study (completion rate 72%). Reasons for discontinuation after randomization included dissatisfaction with group assignment, lack of interest, time constraint, lost to contact, or injury unrelated to study (**Figure 1**). Participants who did not complete the study did not differ significantly in any baseline anthropometric variables from those who completed the study.

Average attendance at exercise sessions in study completers was 90% (SD: ± 10%) and did not differ ($P > .1$) by exercise group (aerobic exercise: 91%, resistance exercise: 89%, and combined: 89%). The average (±SD) aerobic exercise intensity did not differ ($P > .1$) between the aerobic exercise and the combined groups (60.9 ± 8.7% of peak VO_2 vs 57.2 ± 10.8% of peak VO_2), and the average heart rate per session was 145.6 ± 8.7 bpm and 146.1 ± 11.9 bpm in the aerobic exercise and the combined group, respectively. However, due to longer duration of aerobic exercise regimen (aerobic exercise group: 60 min/session vs combined group: 30 min/session), average EE during aerobic exercise sessions was greater ($P < .01$) in the aerobic exercise group compared with the combined group (451 ± 131 kcal/session vs 206 ± 49 kcal/session).

Baseline Characteristics

There were no significant differences between groups with respect to age, anthropometric measurements, total fat, liver fat, skeletal muscle composition, and cardiorespiratory fitness and muscular strength (**Table II**). The R_d (mg/kg/min) tended to be greater ($P = .05$) in the combined exercise group compared with the aerobic exercise group. However, when the whole-body glucose disposal rate was expressed per FFM, no significant differences were found among groups.

Table II. Subject characteristics at baseline

Variables	Aerobic exercise (n = 38)	Resistance exercise (n = 40)	Combined exercise (n = 40)
Male/female, n	13/25	15/25	14/26
Race, n			
Black	18	26	19
White	18	11	12
Mixed	2	1	6
Other	0	2	3
Age, y	14.4 ± 1.6	14.4 ± 1.6	14.5 ± 1.7
Tanner stage*			
II-III	5	6	6
IV-V	33	33	34
Height, cm	167.2 ± 8.1	165.4 ± 9.1	166.3 ± 8.2
Weight, kg	94.9 ± 16.3	91.9 ± 16.8	89.9 ± 16.1
BMI, kg/m²	33.7 ± 4.0	33.4 ± 3.8	32.3 ± 4.1
BMI, percentile	98.3 ± 1.7	98.3 ± 1.2	97.5 ± 2.6
Waist circumference, cm	108.4 ± 10.3	108.1 ± 10.6	105.8 ± 10.7
DXA			
Total fat, %	42.3 ± 5.2	42.4 ± 4.5	41.5 ± 5.1
Total fat, kg	40.3 ± 9.2	38.9 ± 8.9	37.4 ± 8.9
FFM, kg	54.1 ± 9.0	52.5 ± 9.6	52.2 ± 9.5
Liver fat, %	2.5 ± 2.4	3.0 ± 5.1	2.2 ± 2.6
Skeletal muscle composition			
IMAT, cm²	48.2 ± 19.5	47.8 ± 18.0	44.0 ± 18.7
Thigh subcutaneous fat, cm²	332.1 ± 105.5	312.8 ± 88.5	318.5 ± 80.4
Muscle attenuation, HU	52.5 ± 3.0	52.2 ± 2.6	53.0 ± 2.4
Fitness			
Cardiorespiratory fitness, mL/kg/min	23.0 ± 3.6	22.9 ± 4.1	23.5 ± 4.5
1-RM chest press, kg	44.8 ± 18.0	44.7 ± 18.0	44.9 ± 16.1
1-RM leg press, kg	86.5 ± 36.0	92.1 ± 39.1	88.9 ± 30.1
Muscular strength index	1.4 ± 0.5	1.5 ± 0.4	1.5 ± 0.4
Metabolic profiles			
Fasting glucose, mg/dL	92.2 ± 7.1	91.0 ± 8.3	92.0 ± 7.7
2-h glucose, mg/dL	128.7 ± 22.0	118.6 ± 22.3	119.7 ± 21.1
R_d, mg/kg/min†	5.6 ± 1.9	6.4 ± 2.3	6.9 ± 2.6
R_d, mg/kg·FFM/min	9.8 ± 3.2	11.1 ± 3.8	11.7 ± 3.9
Energy intake, kcal/d	1950 ± 482	2108 ± 591	2103 ± 613

DXA, dual-energy X-ray absorptiometry; *HU*, Hounsfield Unit; *RM*, Repetition Maximum.
Data are means ± SD unless otherwise noted. Liver fat: n = 36 in aerobic exercise and n = 38 in combined groups. R_d: n = 39 in resistance exercise and n = 39 in combined groups.
*One subject's Tanner stage was missing in resistance exercise.
†$P = .05$ between groups.

Changes in Primary Outcome

R_d increased significantly in all groups (**Table III**). The improvement in R_d in the aerobic exercise group was greater ($P < .05$) than in the resistance exercise group (1.7 ± 0.1 vs 0.7 ± 0.1 mg/kg/min) but not different from the combined group (1.2 ± 0.1 mg/kg/min). After we accounted for the differences in FFM, the improvements in R_d was still greater in the aerobic exercise group than in the resistance exercise group (2.2 ± 0.1 vs 0.8 ± 0.1 mg/kg·FFM/min, $P < .05$) (**Figure 2**, A). Collapsed across groups, the improvement in R_d was associated ($P < .05$) with reductions in body weight ($r = -0.53$), percent body fat ($r = -0.58$), liver fat ($r = -0.32$), and IMAT ($r = -0.25$).

Table III. Changes in study outcome variables using intent-to-treat analysis

Variables	Study group, mean ± SE			Pairwise significance*		
	Aerobic exercise (n = 38)	Resistance exercise (n = 40)	Combined exercise (n = 40)	Aerobic vs resistance	Aerobic vs combined	Resistance vs combined
Weight, kg	−4.0 ± 0.5†	−1.1 ± 0.5	1.0 ± 0.5	NS	$P < .05$	NS
BMI, kg/m^2	−1.4 ± 0.1†	−0.4 ± 0.1	−0.4 ± 0.1	NS	NS	NS
BMI percentile	−1.0 ± 0.1†	−0.6 ± 0.1†	−0.7 ± 0.1†	NS	NS	NS
Waist circumference, cm	−3.2 ± 0.2†	−1.6 ± 0.2	−1.6 ± 0.2	NS	NS	NS
DXA						
Total fat, %	−2.3 ± 0.2†	−2.0 ± 0.19†	−1.7 ± 0.2†	NS	NS	NS
Total fat, kg	−3.7 ± 0.3†	−2.1 ± 0.3	−0.9 ± 0.3	NS	$P < .05$	NS
FFM, kg	−0.1 ± 0.2	0.9 ± 0.2	2.2 ± 0.3†	NS	$P < .05$	NS
Liver fat, %	−0.61 ± 0.03†	−0.27 ± 0.03	−0.62 ± 0.03†	NS	NS	NS
Skeletal muscle composition						
IMAT, cm^2	−10.7 ± 0.2†	−8.5 ± 0.2†	−7.2 ± 0.2†	NS	NS	NS
Thigh subcutaneous fat, cm^2	−40.5 ± 3.2†	−15.7 ± 3.2	−8.4 ± 3.4	NS	$P < .05$	NS
Muscle attenuation, HU	1.19 ± 0.03†	1.07 ± 0.03†	0.64 ± 0.03†	NS	NS	NS
Fitness						
Cardiorespiratory fitness, mL/kg/min	5.5 ± 0.2†	2.1 ± 0.2†	5.4 ± 0.2†	$P < .05$	NS	$P < .05$
1-RM chest press, kg	6.8 ± 0.4†	26.7 ± 0.4†	18.8 ± 0.4†	$P < .05$	$P < .05$	$P < .05$
1-RM leg press, kg	20.0 ± 0.4†	32.5 ± 0.4†	31.6 ± 0.4†	NS	NS	NS
Muscular strength index	0.35 ± 0.01†	0.73 ± 0.01†	0.57 ± 0.01†	$P < .05$	$P < .05$	NS
Metabolic profiles						
Fasting glucose, mg/dL	−0.5 ± 0.2	−1.6 ± 0.2	0.9 ± 0.2	NS	NS	NS
2-h glucose, mg/dL	−8.2 ± 0.5†	−12.8 ± 0.5†	−10.4 ± 0.5†	NS	NS	NS
R_d, mg/kg/min	1.7 ± 0.1†	0.7 ± 0.1†	1.2 ± 0.1†	$P < .05$	NS	NS
R_d, mg/kg·FFM/min	2.2 ± 0.1†	0.8 ± 0.1	1.5 ± 0.1†	$P < .05$	NS	NS
Energy intake, kcal/d	133 ± 16	−288 ± 16†	−206 ± 18†	$P < .05$	$P < .05$	NS

Values are expressed as predicted means and SE of differences in preintervention vs postintervention values adjusting for age and sex. The missing data in the 6-month outcomes were imputed using conditional mean method on the treatment status, baseline age, and sex.
*Pairwise comparisons of changes in outcome variables using general linear regression models adjusted for age and sex.
†Significant preintervention vs postintervention differences within group, $P < .05$. *NS*, not significant $P > .05$.

Fasting glucose levels did not change in any of the exercise groups. However, there were significant reductions ($P < .05$) in 2-hour glucose level in all groups, and these reductions were not different ($P > .05$) between exercise groups (**Figure 2**, B).

Changes in Secondary Outcomes

A moderate but significant weight loss was observed in the aerobic exercise group (−4.0 ± 0.5 kg), and the change in body weight in the aerobic exercise group was greater ($P < .05$) than those in the combined group (1.0 ± 0.5 kg) (**Table III**). Significant reductions in BMI (−1.4 ± 0.1 kg/m^2) and waist circumference (−3.2 ± 0.2 cm) were observed in the aerobic exercise group only. Total adiposity (%) was reduced ($P < .05$) in all groups by a similar magnitude. However, the reduction in total fat mass (kilograms) was significantly greater in the aerobic exercise than those in the combined group.

Liver fat was reduced ($P < .05$) within the aerobic exercise (−0.61 ± 0.03%) and combined (−0.62 ± 0.03%) group but not in the resistance exercise group (−0.27 ± 0.03%, $P > .05$). IMAT was reduced ($P < .05$) within all groups, but these changes were not different between groups. Muscle attenuation (HU) increased ($P < .05$) in all groups by a similar magnitude.

Cardiorespiratory fitness and muscular strength index increased ($P < .05$) independent of exercise group. The increases in cardiorespiratory fitness in the aerobic exercise and combined exercise groups were greater ($P < .05$) than those in the resistance exercise group. Compared with the aerobic exercise group, the improvements in muscular strength index was greater ($P < .05$) in the resistance exercise and the combined exercise groups. Total energy intake assessed by 24-hour dietary recall was reduced ($P < .05$) in the resistance exercise and combined groups and not in the aerobic exercise group.

Discussion

We examined whether a combined aerobic and resistance exercise is more effective than either aerobic exercise or resistance exercise alone (without caloric restriction) in improving insulin sensitivity and reducing liver fat and skeletal muscle lipid in previously sedentary adolescents with overweight or obesity. Our results demonstrate that all 3 types of regular exercise are beneficial in reducing percent body fat and skeletal muscle lipid and improving insulin sensitivity, OGTT 2-hour glucose, and fitness levels (both cardiorespiratory fitness and muscular strength); combined aerobic exercise and resistance exercise and aerobic exercise alone are equally effective in reducing ectopic fat in the liver and skeletal muscle and improving insulin sensitivity and OGTT 2-hour glucose level; and aerobic exercise is more effective than resistance exercise at improving insulin sensitivity.

Although it is well accepted that regular exercise confers substantial health benefits, the optimal mode of exercise for reducing T2DM risk is unclear in youth. A meta-analysis reported that in youth with overweight and obesity, aerobic exercise typically is associated with reductions in fasting insulin and homeostatic model assessment of insulin resistance compared with

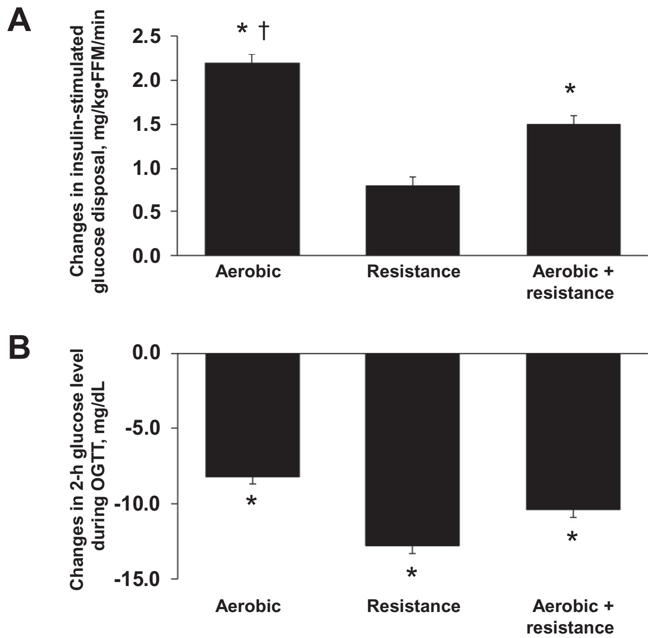

Figure 2. **A,** Improvements in insulin-stimulated glucose disposal within group. Data are shown as predicted means and SE of differences in preintervention vs postintervention values adjusting for age and sex. *Significant preintervention vs postintervention differences within group, $P < .05$. †Significant preintervention vs postintervention differences compared with the resistance group, $P < .05$. **B,** Reductions in 2-hour glucose level during a 2-hour oral glucose tolerance test within group. Data are shown as predicted means and SE of differences in preintervention vs postintervention values adjusting for age and sex. *Significant preintervention vs postintervention differences within group, $P < .05$.

the control.[26] In 1 study, the effects of all 3 exercise modalities (aerobic exercise, resistance exercise, and combined aerobic and resistance exercise) were evaluated in the pediatric populations. Sigal et al examined the effects of caloric restriction (daily energy deficit 250 kcal) with either aerobic exercise, resistance exercise, or combined exercise on total fat (%) and cardiometabolic risk factors in obese adolescents.[27] In that study,[27] all exercise groups similarly reduced total adiposity (−1.1% in the aerobic exercise, −1.6% in the resistance exercise, and −1.4% in the combined group), but no significant group differences were found in fasting glucose and 2-hour glucose levels. The present study randomized trial examined the independent and the combined effects of aerobic exercise and resistance exercise on insulin sensitivity and ectopic fat in the liver and skeletal muscle using the gold standard methods, including hyperinsulinemic-euglycemic clamp, ^{1}H-MRS and computed tomography in the pediatric population. Our findings extend the previous finding by Sigal et al and provide evidence that, in the absence of caloric restriction, combined aerobic and resistance exercise and aerobic exercise alone are similarly effective in improving insulin sensitivity and OGTT 2-hour glucose and aerobic exercise alone is superior to resistance exercise alone in improving insulin sensitivity in adolescents with overweight and obesity.[27]

Unlike the previous studies in adults reporting greater improvements in T2DM risk factors in response to the combined exercise than either exercise alone,[8-10] we did not find substantial benefits of adding resistance exercise to a moderate-intensity aerobic exercise in improving insulin sensitivity in obese adolescents. Although this discrepancy is uncertain, it is important to note that in these adult studies,[8,10] exercise duration was significantly longer in the combined exercise group than either exercise alone group. Therefore, it is unclear whether greater improvements in insulin resistance observed in response to the combined aerobic exercise and resistance exercise regimen are due to a synergistic effect of aerobic exercise and resistance exercise or simply due to a greater exercise volume.

We observed that for a similar exercise duration (approximately 180 min/wk), aerobic exercise alone is more effective than the combined exercise in reducing body weight and total fat mass in adolescents with overweight and obesity. The greater reductions in body weight and total fat in response to aerobic exercise alone vs combined exercise could be due to the differences in EE between groups, as oxygen consumption during resistance exercise is estimated to be less than 50% of maximal VO_2.[28] Our findings that, collapsed across groups, the improvement in insulin-stimulated glucose disposal was significantly associated with reductions in body weight, total adiposity, liver fat, and IMAT reinforce the importance of reducing total adiposity and ectopic fat in the liver and muscle to improve insulin sensitivity in adolescents with overweight and obesity. These findings suggest that for overweight and obese adolescents who want to lose weight and improve insulin resistance and fatty liver, aerobic exercise may be the most effective and time-efficient exercise strategy.

It has been suggested that skeletal muscle is the major site for whole-body R_d.[29] Skeletal muscle of adults with obesity and T2DM is characterized by reduced muscle attenuations and an increased IMAT as compared with normal-weight individuals and both reduced muscle attenuation and increased IMAT are associated with insulin resistance.[30] Similarly, we previously demonstrated that both IMAT and muscle attenuation are significantly associated with total adiposity in children and adolescents.[14] Our current study demonstrates that regular exercise independent of exercise modality is effective in reducing IMAT and increasing muscle attenuation and highlights the importance of regular exercise as a strategy to reduce skeletal muscle lipid in adolescents with overweight and obesity.

In this study, cardiorespiratory fitness increased in all 3 exercise modalities, and the increases in the aerobic exercise and the combined groups were significantly greater than those in the resistance exercise group. With respect to muscular fitness, although all groups increased whole-body muscular strength index, the greatest improvement was observed in the resistance exercise group. Based on these observations, we recommend that adolescents with overweight and obesity who want to maximize muscular strength and fitness should incorporate resistance exercise in their intervention strategies.

The strengths of our study include the randomized study design, including 3 exercise interventions in the same study, excellent adherence to the exercise regimens (90%), direct supervision of all exercise training sessions with automated monitoring of heart rate during each aerobic exercise session and monitoring of proper form and technique during each resistance exercise session, and measuring insulin sensitivity and ectopic fat content using the-state-of-the-art methodologies such as the 3-hour hyperinsulinemic–euglycemic clamp and ^{1}H-MRS techniques.

The limitations of this study warrant mention. Our study consists of predominantly black and white adolescents. Whether similar findings would be observed in other ethnic groups (eg, Asian youth) and youth with T2DM and other metabolic conditions is unknown. We did not include the nonexercising control group, as the goal of the study was to examine whether the combined aerobic and resistance exercise is more effective than either exercise alone in reducing obesity-related health risk factors, and the benefits of regular exercise compared with nonexercising controls were clearly documented in obese youth. Further, 64% of our study participants was female and, because of small sample size, we were unable to examine the influence of sex and race on the changes in insulin sensitivity in response to different exercise modalities. Currently, it is unknown whether differing distributions of male and female subjects played a role in our findings. Lastly, our findings may not be generalized to the general population of adolescents with overweight and obesity because exercise training sessions, access to exercise facilities, and diet counseling were offered for 6 months at no cost, which may have helped to improve exercise compliance.

In conclusion, we found that all 3 exercise modalities are beneficial in reducing total fat and skeletal muscle lipid and improving risk factors for T2DM (insulin sensitivity and OGTT 2-hour glucose level) in adolescents with overweight and obesity. The data observed here demonstrate important public health implications for understanding the benefits of different exercise modalities and provide therapeutic strategies to health-care professionals when prescribing the optimal exercise interventions to improve specific health outcomes of interest in adolescents with overweight and obesity. ■

We thank the study participants and their parents, the Weight Management and Wellness Center research staff (Nicole Mullarkey, Jenna Spector, Nancy Guerra, Resa Stauffer), and many undergraduate and graduate students in the Department of Health and Physical Activity at the University of Pittsburgh.

Submitted for publication Jul 31, 2018; last revision received Sep 24, 2018; accepted Oct 25, 2018

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50 Years Ago in *The Journal of Pediatrics*

Serum Immunoglobulin Levels in Newborn Infants I: Evaluation of a Radial Diffusion Plate Method

McCracken GH, Jr, Chen TC, Hardy JB, Tzan N. J Pediatr 1969;74:378-82

In this report, McCracken et al describe the laboratory methodology and performance characteristics of the quantitative radial diffusion agar plate technique for measurement of neonatal cord blood IgM levels. Congenital infections, including rubella, were prevalent and the specificity of elevated total neonatal IgM levels as signifying infection in utero was known. A simple test, available to clinical laboratories, would be a boon for the diagnosis of congenital infections as well as for furthering an understanding of their epidemiology, burden of disease, and management. In this method, dilutions of test sera were pipetted into wells cut in agar imbedded with antiserum. The diameter of the precipitin ring around test wells was measured and compared with a curve derived from a reference standard. Although concluding positively, the authors described what continue to this day to be pitfalls in the reproducibility of the measurement of total and pathogen-specific IgM levels for diagnostic purposes. Much but not all of the laboratory limitations are related to substantial variation in measurement of the typically low concentrations of IgM antibody as well as in day-to-day quantitative variation in test results.

The first author on this paper, George H. McCracken, Jr, at the time was a research associate at the National Institute of Child Health and Human Development in the Perinatal Research Branch and Office of Biometry. The "perinatal" and "research" part would stick with Dr McCracken, as he went on to contribute as did none other to the evidence base for the pathogenesis and management of neonatal gram-negative bacillary meningitis, as well as that of bacterial meningitis beyond the neonatal period, and to the development and optimal use of antibiotics broadly for infectious diseases. Dr McCracken also contributed remarkable time and effort to nurture the careers of countless young clinicians and investigators (including this writer) in pediatric infectious diseases, a field that would not become an American Board of Pediatrics subspecialty for another 25 years. And then he took (reporting "the worst headache of my life") and passed the first certifying examination, much to the relief of himself and this writer, his grateful student, who chaired with trepidation the writing of the first certifying examination that was given concurrently to grand masters and newbies.

At Dr McCracken's retirement, we all share in the collective applause of the subspecialty, of academic medicine, and of generations of children whose care has been impacted by his work.

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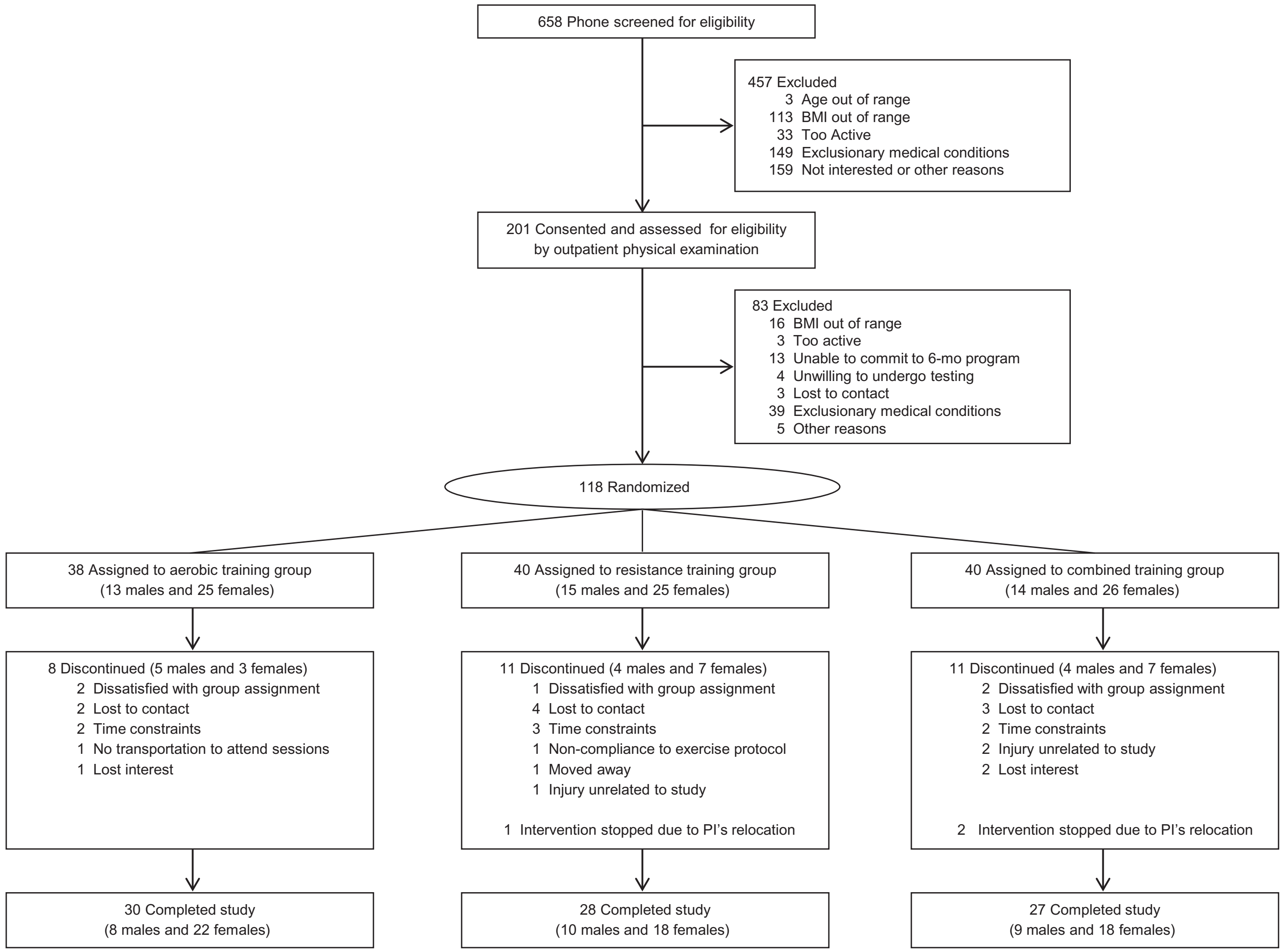

Figure 1. Participant flow diagram. All subjects assigned to each treatment (including those who discontinued the study) were included in intent-to-treat analyses.

Table I. Description of exercise interventions

<table>
<tr><th>Description of exercise interventions</th><th>Aerobic exercise</th><th>Combined exercise</th><th>Resistance exercise</th></tr>
<tr><td>No. weekly exercise sessions</td><td>3</td><td>3</td><td>3</td></tr>
<tr><td>Type of exercise</td><td></td><td></td><td></td></tr>
<tr><td>Aerobic</td><td>60 min</td><td>30 min</td><td>None</td></tr>
<tr><td></td><td colspan="2">Moderate intensity (measured heart rate* to ensure 50% 65% of peak VO_2†) using a treadmill or an elliptical machine</td><td></td></tr>
<tr><td>Resistance‡</td><td></td><td>1 set (30 min per session)</td><td>2 sets (60 min per session)</td></tr>
<tr><td></td><td>None</td><td colspan="2">Eight exercises (12-15 reps per set) using weight machines, each to volitional fatigue: leg press, leg extension, leg flexion, chest press, latissimus pull down, seated row, bicep curl, and triceps extension. Modified push-ups and abdominal crunches to exhaustion.</td></tr>
<tr><td>Total weekly exercise duration</td><td>180 min</td><td>180 min</td><td>180 min</td></tr>
</table>

*Aerobic exercise intensity was monitored every 5 minutes using an automated heart rate monitor (Polar Oy).
†Obtained from graded maximal treadmill test.
‡Proper lifting techniques was emphasized and when subjects were able to perform 15 repetitions at a given weight with a proper form, the weight was gradually increased to maintain adequate loads within 12-15 repetition ranges.