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Aerobic exercise but not resistance exercise reduces intrahepatic lipid content and visceral fat and improves insulin sensitivity in obese adolescent girls: A randomized controlled trial

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ABSTRACT

It is unclear whether regular exercise alone (no caloric restriction) is a useful strategy to reduce adiposity and obesity-related metabolic risk factors in obese girls. We examined the effects of aerobic (AE) versus resistance exercise (RE) alone on visceral adipose tissue (VAT), intrahepatic lipid and insulin sensitivity in obese girls. Forty-four obese adolescent girls (BMI $\geq 95^{th}$, 12-18 yrs) with abdominal obesity (waist circumference 106.5 ± 11.1 cm) were randomized to 3-months of 180 min/week AE (*n*=16) or RE (*n*=16) or a non-exercising control group (*n*=12). Total fat and VAT were assessed by MRI and intrahepatic lipid by proton magnetic resonance spectroscopy. Intermuscular AT (IMAT) was measured by CT. Insulin sensitivity was evaluated by a 3-hour hyperinsulinemic (80 mU/m^2/min)-euglycemic clamp.

Compared with controls (0.13 ± 1.10 kg), Body weight did not change (*P*>0.1) in the AE (-1.31 ± 1.43 kg) and RE (-0.31 ± 1.38 kg) groups. Despite the absence of weight loss, total body fat (%) and IMAT decreased (*P*<0.05) in both exercise groups compared with control. Compared with control, significant (*P*<0.05) reductions in VAT (Δ -15.68 ± 7.64 cm^2) and intrahepatic lipid (Δ -1.70 ± 0.74%), and improvement in insulin sensitivity (Δ 0.92 ± 0.27 mg/kg/min per μU/ml) were observed in the AE group, but not the RE group. Improvements in insulin sensitivity in the AE group were associated with the reductions in total AT mass (*r* = -0.65, *P*=0.02). In obese adolescent girls, aerobic exercise, but not resistance exercise is effective in reducing liver fat, visceral adiposity and improving insulin sensitivity independent of weight loss or calorie restriction.

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Key word: insulin sensitivity, intrahepatic lipid, visceral fat, exercise, adolescents

INTRODUCTION

The epidemic rate of childhood obesity is a major health concern in the United States as overweight and obese youth are at increased risk of developing co-morbidities such as non-alcoholic fatty liver disease (35), type 2 diabetes (33) and metabolic syndrome (21, 41), once considered diseases of adulthood. Although both diet and physical activity are considered the first line of approach to treat obese youth (9), we recently reported that in obese adolescent boys increasing physical activity alone, independent of calorie restriction, is beneficial to reduce total fat, visceral adiposity and intrahepatic lipid, and improves cardiorespiratory fitness (CRF) (22). In obese adolescent girls, the utility of exercise alone as a strategy for reducing obesity-related metabolic risk factors is currently unclear. Given the lower physical activity levels in girls than in boys (14), and that physical activity declines substantially in girls during adolescence (17), we conducted a randomized controlled trial to examine the role of regular exercise alone (i.e. no calorie restriction) in reducing obesity-related risk factors in previously sedentary obese adolescent girls. Specifically, we compared the effects of aerobic (AE) versus resistance exercise (RE) on insulin sensitivity, visceral adipose tissue (VAT), and ectopic fat depositions in the liver and skeletal muscle.

MATERIALS AND METHODS

Subjects

The study (ClinicalTrials.gov Identifier: NCT01323088) was conducted from August, 2010 through October, 2012 at Children's Hospital of Pittsburgh (CHP). Obese [BMI $\geq$ 95th percentile (30)] black and white girls were recruited via flyers posted in the city public transportation system and posters placed on campus, and from the Weight Management and Wellness Center at CHP. Inclusion criteria included that the subjects be 12-18 years of age, pubertal (Tanner Stages III-V), non-smokers, non-diabetic, and physically inactive (no participation in structured physical activity for the past three months except school physical education classes). Exclusion criteria included recent significant weight change (BMI >2-3 kg/m^2), musculo-skeletal injuries, endocrine disorders (e.g., polycystic ovary syndrome, type 2 diabetes), syndromic obesity, pregnancy, psychiatric disorders and use of chronic medications that are known to influence glucose metabolism or body composition. Girls with oral or injectable contraceptives were also excluded. Participants self-identified as black or white. A complete medical history, physical examination and pubertal development were assessed according to Tanner criteria (37) by a certified nurse practitioner. The investigation was approved by the University of Pittsburgh Institutional Review Board. Parental informed consent and child assent were obtained from all participants before participation. All participants underwent routine hematological and biochemical tests at the Pediatric Clinical and Translational Research Center (PCTRC) at CHP.

Randomization

Randomization was performed after completing baseline evaluation. Similar to our previous study (22), random assignment to one of three interventions, AE, RE or a non-exercising control group was performed by lottery using a completely randomized design and cell sizes of 16.

Exercise regimen

The exercise groups exercised at either the downtown Pittsburgh YMCA exercise facility or the exercise laboratory at CHP for 3 months. All exercise sessions were by appointment and supervised by exercise physiology graduate students. Participants in the AE group exercised three times per week, for 60 minutes/session (including 5 min warm-up and 5 min cool-down), using treadmills and/or ellipticals. AE programs progressively increased in duration and intensity, beginning at 40 min at ~50% of VO_{2peak}, increased up to 60 min at 60-75% of VO_{2peak} by week two. Participants wore a heart rate monitor (Polar Oy, Kempele, Finland) during the exercise sessions to ensure achievement of the target heart rate. The heart rate range associated with 60-75% of VO_{2peak} was determined from the baseline maximal oxygen uptake test for each subject. Energy expenditure was estimated using the heart rate-VO_2 relationship observed during the VO_{2peak} test.

The RE group performed a series of 10 whole body exercises, three times per week, for 60 minutes/session. Each training session included leg press, leg extension, leg flexion, chest press, latissimus pull down, seated row, bicep curl and tricep extension using stack weight equipment. In addition, a single set of push-ups and sit-ups were performed. For the first four weeks, participants performed 1-2 sets of 8-12 repetitions at 60% of baseline 1RM (repetition

maximum) with proper lifting techniques. During weeks 4 ~ 13, subjects performed 2 sets of 8-12 repetitions to fatigue.

Control subjects were asked not to participate in structured physical activities throughout the study. To maintain adherence, participants were given the opportunity to participate in exercise sessions following the completion of post-intervention evaluations.

Dietary regimen

All participants were asked to follow a weight maintenance diet (55-60% carbohydrate, 15-20% protein, and 25-30% fat) throughout the study to be able to assess the effects of regular exercise alone on insulin sensitivity and fat distribution. Daily energy requirements to maintain baseline body weight were determined at baseline by estimating resting energy expenditure and multiplying the obtained value by a factor of 1.2 (12)

Anthropometrics

Body weight was measured to the nearest 0.1 kg and height was measured to the nearest 0.1 cm. Waist circumference was measured at the top of the iliac crest and the average of two measurements was used in the analyses.

Oral glucose tolerance test

Participants reported to the PCTRC after an overnight fast for a 2-hour oral glucose tolerance test (OGTT, 1.75 g/kg, max 75 g). Blood samples were obtained at -15, 0, 15, 30, 60, 90 and 120 minutes for determination of glucose and insulin levels. Glucose and insulin area

under the curve (AUC) was determined using a trapezoid model (2). Participants remained in the PCTRC and stayed overnight at CHP to undergo the euglycemic clamp test the next morning.

Measurement of insulin sensitivity

Fasting endogenous glucose production was measured with a primed (2.2 μmol/kg) constant-rate infusion of [6, 6-$^2H_2$]glucose (Isotech, Miamisburg, OH) from 0730–0930 h as shown by us previously (4). Blood was sampled at the start of the stable isotope infusion (-120 min) and every 10 min from -30 to 0 min (basal period) for determination of plasma glucose, insulin, and isotopic enrichment of glucose. Fasting hepatic glucose production (HGP) was calculated during the last 30 min. (-30 to time zero) of the basal 2-h infusion period. Fasting hepatic insulin sensitivity was calculated as the inverse of the product of hepatic glucose production and fasting plasma insulin concentration (1,000/HGP x fasting plasma inulin) as shown previously (4). After the 2-h baseline isotope infusion period, insulin-mediated glucose uptake and insulin sensitivity were measured during a 3-h hyperinsulinemic-euglycemic clamp from 0930-1230 h. Intravenous crystalline insulin (Humulin; Lilly Indianapolis, IN) 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 every 5 min. Peripheral insulin sensitivity was calculated by dividing insulin-stimulated glucose disposal rate by the steady-state plasma insulin concentration during the last 30 min of the clamp. In the exercise groups, post-exercise clamp test was performed 48-72 hours post-exercise session to control for the effects of acute exercise on glucose uptake (31). One subject in the aerobic group did not complete the post-intervention clamp due to difficulty with IV access. One control subject's post-intervention clamp test ended early due to IV issues and her glucose disposal rate

166 at 80 min was used to calculate insulin sensitivity. Among study completers (*n*=36), 14 subjects
167 and 19 subjects were examined in the luteal and follicular phase, respectively at baseline and 17
168 subjects and 16 subjects were examined in the luteal and follicular phase, respectively at follow-
169 up. The phase of the menstrual cycle was not determined in three subjects who had irregular
170 menstrual cycle at both time points.
171
172 *Biochemical measurements*
173 Plasma glucose was measured by the glucose oxidase method with a glucose analyzer
174 (YSI, Inc., Yellow Springs, OH), and the insulin concentration was determined by
175 radioimmunoassay (3).
176
177 *Total adipose tissue (AT), skeletal muscle and abdominal AT*
178 Whole-body magnetic resonance imaging (MRI) was obtained with a 3.0 Tesla magnet
179 (Siemens Medical Systems, Erlangen, Germany) using our standard protocol (25). One subject
180 in the control group (post measurement) and in the AE group (both pre and post measurement)
181 did not complete MRI and ^{1}H-MRS due to claustrophobia.
182
183 *Intrahepatic lipid by proton magnetic resonance spectroscopy (^{1}H-MRS)*
184 ^{1}H-MRS was performed with a 3.0 Tesla MR system (Siemens, Tim Trio, Erlangen,
185 Germany) using a body matrix coil and a spine matrix (Siemens, Erlangen, Germany) using our
186 standard protocol (22). A voxel (30 x 30 x 20 mm^3) was placed avoiding blood vessels and
187 intrahepatic bile ducts, using the following parameters (TR = 4000 ms, TE = 30 ms). Eight
188 acquisitions were recorded in a measuring time of 32 sec without water suppression and the

average of eight spectra was used for intrahepatic lipid (%) calculation as shown below. Spectra were fitted using the AMARES algorithm in the Java-based magnetic resonance user interface (jMRUI) software package (28). Absolute concentrations of intrahepatic lipid (CH_2) were obtained from the area under the curve of the methylene signals of lipids at 1.3 ppm, using tissue water content as an internal reference. One subject (AE)'s baseline data was excluded due to motion artifact.

$$\text{Intrahepatic lipid (\%)} = \frac{\text{lipid peak}}{\text{water peak + lipid peak}} \text{ X } 100$$

Intermuscular adipose tissue (IMAT) by computed tomography (CT)

Mid-thigh CT images were obtained on a GE CTI-Helical Scanner (GE Medical Systems, Milwaukee, Wisconsin) using 170 mA, 120 kV, a 512 X 512 matrix, and 48-cm field of view using our standard protocol (23). IMAT area was defined as AT area beneath the fascia lata surrounding skeletal muscle and AT area between muscle bundles as shown previously (11).

Cardiorespiratory fitness (CRF) and muscular strength

CRF was determined using a graded treadmill test with the use of standard open-circuit spirometry techniques (AEI Technologies, Pittsburgh) until volitional fatigue using our standard protocol (22). Muscular strength was assessed with a one-repetition maximum (1RM) test for the supine chest press and seated leg press using weight stack equipment (Life fitness, Schiller Park, IL). Muscular strength index was calculated as the sum of the 1RM scores for the chest and leg press expressed per kg of body weight (16).

Statistical Analysis

A one-way analysis of variance (ANOVA) and ANCOVA adjusting for BMI and race were performed to examine group differences at baseline. When the ANOVA *P*-value was <0.05, a Tukey's post hoc comparison test was used to locate group differences. We examined the effect of the intervention using an intent-to-treat analysis for only randomized subjects with baseline data. Missing follow-up data values were estimated using multiple-imputations procedure (Proc MI) with 100 imputations (27). Repeated measures analysis of covariance was used to determine treatment change differences for each variable using the imputed data with adjustment for baseline values for that variable. We also examined the effect of the exercise intervention using as-treated analyses in participants who had complete baseline and follow-up data. Least squared means difference post hoc tests were used to determine differences between the control and intervention groups. The relationships between changes in total and abdominal fat, and insulin sensitivity were evaluated by Pearson correlations coefficients.

P values of less than 0.05 were accepted to indicate statistical significance. All analyses were performed using commercially available software (SAS, version 9.2; SAS Institute Inc, Cary, North Carolina). Unless otherwise indicated, data are expressed as mean (SE).

RESULTS

Baseline characteristics

Baseline subject characteristics are shown in **Table 1.** Fasting insulin, insulin AUC, insulin sensitivity and VO_{2peak} were lower ($P<0.05$) in the RE group compared with the AE group. However, these differences did not remain significant ($P>0.05$) after adjusting for BMI and race.

Adherence to the exercise programs

Of the 44 obese girls randomized, 37 completed their assigned treatment (**Figure 1**). We excluded one control subject from data analyses who was dissatisfied with the group assignment and was intentionally reducing calorie intake during the study. Average (± SD) attendance at the exercise sessions was 95% (± 4.3%) in the AE and 97% (± 2.8%) in the RE groups and average exercise duration was similar between the AE (56.0 ± 1.1 minutes/session) and RE (57.0 ± 0.7 minutes /session) group. In the AE group, the average heart rate was 153.0 ± 6.6 bpm and energy expenditure was 536.6 ± 72.9 kcal/session.

Changes in CRF and muscular strength

Compared with the non-exercising control group, CRF increased ($P<0.05$) by 17 % in the AE group, but not in the RE group (**Table 2**). Muscular strength increased ($P<0.05$) in the RE group (45%) only by comparison to controls.

Changes in total adiposity and skeletal muscle

Body weight, BMI and waist circumference did not change (P>0.1 for all) in either exercise groups (**Table 2**). Compared with controls, a significant reduction (P<0.05) in % body fat was observed within the AE (-1.70 ± 0.85%) and RE (-1.63 ± 0.78%) groups. Skeletal muscle mass did not change within any of the exercise groups (P>0.05).

Changes in VAT, intrahepatic lipid and IMAT

Compared with controls, significant (P<0.05) reductions in VAT (Δ -15.68 ± 7.64 cm^2) and intrahepatic lipid (Δ -1.70 ± 0.74%) were observed in the AE, but not in the RE group (**Table 2**). In both AE (Δ -13.5 ± 4.2 cm^2) and RE (Δ -10.9 ± 4.2 cm^2) groups, there were reductions (P<0.05) in IMAT by comparison to controls.

Changes in insulin sensitivity

Compared with controls, fasting glucose production and hepatic insulin sensitivity did not change significantly in the AE and the RE groups (**Table 3**). Peripheral insulin sensitivity improved significantly in the AE group (0.92 ± 0.27 mg/kg/min per μU/ml, P=0.0007), even when insulin sensitivity was expressed per unit of FFM (Δ 1.43 ± 0.44 mg/kg FFM/min per μU/ml, P=0.001), compared with controls (Δ -0.79 ± 0.35 mg/kgFFM/min per μU/ml). These observations remained unchanged when analyses were repeated excluding a control subject whose post-intervention clamp ended early due to IV issues. The improvement in peripheral insulin sensitivity in the AE group was significantly associated with the loss in total AT mass (r = -0.65, P=0.02), but not VAT or intrahepatic lipid (P>0.05). No significant changes in OGTT parameters (such as glucose and insulin levels at 2 hr, and glucose and insulin AUCs) were observed in any groups.

DISCUSSION

The present investigation reveals that in obese adolescent girls, despite the absence of weight loss, significant reductions in percent body fat and IMAT were achieved after 3 months (3 days/weeks) of AE and RE programs. Moreover, AE but not RE was associated with significant reductions in visceral adiposity and intrahepatic lipid, and improvements in insulin sensitivity and CRF. These findings suggest, for the first time, that AE may be a better mode of exercise than resistance exercise in obese adolescent girls to reduce abdominal adiposity and liver fat, and improve insulin resistance.

Although adult studies report the beneficial effects of exercise alone on insulin action in women (8, 32, 34), little information is available regarding the independent role of regular exercise on insulin resistance in adolescent girls. Treuth et al. (38) reported no significant changes in fasting glucose and insulin, and glucose and insulin AUC in response to a 5-month strength training (3 days/week, 20 min/session) in obese prepubertal girls (n=9). By contrast, Nassis et al. (29) demonstrated that 12 weeks of AE without weight loss (3 days/week, 40 minutes/session) resulted in a significant reduction in insulin AUC (23%) in overweight and obese girls (9-15 years, n=19). Using a randomized controlled trial, our findings that AE without calorie restriction and weight loss resulted in significant improvements in insulin sensitivity (33%), assessed by a 3-hr hyperinsulinemic-euglycemic clamp technique, extends previous observations (29, 38) using surrogate measures of insulin sensitivity (OGTT) and provides evidence that engaging in AE alone is an effective means of improving insulin sensitivity in these high risk obese adolescent girls. Additionally, the use of whole-body MRI, ^{1}H-MRS and computed tomography in our study allowed direct assessments of changes in whole-body adipose tissue distribution in response to aerobic exercise versus resistance exercise.

298 Our findings that AE without calorie restriction is associated with significant reductions
299 in intrahepatic lipid and VAT in obese adolescent girls are consistent with van der Heijden et al.
300 (39) who reported that a 12-week AE without calorie restriction (2 days/week, 30 min/session)
301 was associated with reductions in intrahepatic lipid (~37%) and VAT (~9.3%) in a mixed sample
302 of Hispanic obese boys and girls (*n*=15). The current findings with respect to AE are paralleled
303 with our previous observations in obese adolescent boys (22), who showed significant reductions
304 in VAT (7%) and intrahepatic lipid content (40%). However, with respect to RE, the two
305 genders responded differently. Unlike the obese adolescent boys (22), obese girls did not have
306 significant reductions in intrahepatic lipid and VAT in response to RE. Further, unlike the obese
307 adolescent boys (22), we did not find a significant increase in skeletal muscle mass in obese
308 adolescent girls in response to resistance exercise. We are unclear about this observed gender
309 difference in response to resistance exercise as the exercise training regimens and the
310 methodologies (^{1}H-MRS and MRI) were identical in both studies. Perhaps, testosterone in
311 adolescent boys may enhance the benefits of resistance exercise on skeletal muscle mass.
312 It is well-established that visceral fat is a strong risk factor for obesity related co-
313 morbidities in youth (24, 40). Although the underlying mechanisms by which visceral fat is
314 associated with metabolic abnormalities are unclear, it has been hypothesized that excess free
315 fatty acids released from the visceral adipocytes drains directly into the liver via the portal vein,
316 resulting in intrahepatic lipid accumulation, VLDL production and reduced insulin clearance in
317 the liver ("the portal theory") (5). However, in this study, visceral fat and intrahepatic lipid were
318 not associated with both hepatic and peripheral insulin sensitivity in obese adolescent girls.
319 These are different from our previous findings in obese adolescent boys (22), demonstrating that
320 the change in insulin sensitivity was significantly correlated with the corresponding changes in

visceral fat (r= -0.47, P<0.05). Perhaps, gender differences in the amount of visceral fat (lower visceral fat in obese girls vs. obese boys) may explain the strength of the relationships between visceral fat and insulin sensitivity in obese boys vs. obese girls.

There were also gender differences with respect to the change in peripheral insulin sensitivity after the exercise training program. While we observed significant improvements in insulin sensitivity in response to RE in obese adolescent boys (22), the identical RE intervention did not result in improvements in insulin sensitivity in obese adolescent girls. Theoretically, one would expect that cardiometabolic and diabetes risk factors would improve after resistance training. Contrary to the latter, Kirwan (19) showed that eccentric exercise resulted in transient decreases in insulin sensitivity (-37%) in healthy individuals that persists for ~48 h after the exercise bout. It has been suggested that the reductions in insulin sensitivity after eccentric exercise is mediated by increased inflammatory markers related to exercise-induced muscle damage (18). However, as we acquired insulin sensitivity measures with identical protocols in boys and girls, this is unlikely to explain the observed gender contrast in insulin sensitivity following the two different exercise regimens. Alternatively, others report substantial inter-individual variability in the ability to improve health outcomes in response to regular exercise. For example, Bouchard et al. (6) reported that among study completers (n=1,687) from six-exercise intervention trials (HERITAGE family study, DREW, INFLAME, STRRIDE, MARYLAND and JYVASKYLA), 8.4% had adverse changes in fasting insulin, 13.3% for HDL-C and 12.2% for systolic blood pressure after AE independent of age and CRF. It is unknown the degree to which this inter-individual variation in RE response occurs. Furthermore, the possibility that the two sexes may respond differently to various exercise regimens points to the need to individualize the exercise training to gain the most health benefit.

Our finding that both AE and RE is associated with reductions in IMAT in obese adolescent girls is of importance given that IMAT is inversely associated with insulin sensitivity in adolescents (23). That regular exercise is effective in reducing IMAT in obese girls is consistent with adult studies (13, 26), demonstrating the beneficial effects of exercise in reducing skeletal muscle lipid content measured by CT. However, these observations differ from studies employing ^{1}H-MRS, which report no significant changes in intramyocellaur lipid (IMCL) in response to regular exercise in obese adolescents (22, 39) and obese adults (15). Although both CT and ^{1}H-MRS methods have been used in clinical research for assessing skeletal muscle lipid *in vivo*, it is important to note that IMAT measured by CT and IMCL measured by ^{1}H-MRS do not equate. Although CT is unable to differentiate between IMCL and extramyocellular lipids (EMCL), it measures a larger muscle group and muscle attenuation measured by CT as an overall lipid marker is more reproducible than EMCL or IMCL measured separately by ^{1}H-MRS (20).

Similar to our previous study in obese boys (22), obese adolescent girls complied well with the prescribed exercise training regimen resulting in high attendance rates. However, anecdotally, the girls in the RE group did not enjoy the treatment intervention as much as the AE group. Interestingly, this was the opposite sentiment given by obese boys. Therefore, given the superior improvements in metabolic health with aerobic exercise and the enjoyment factor, we propose that AE may be a better mode of exercise for adolescent girls of this age group.

The current physical activity guidelines from the U.S. Department of Health and Human Services (2008) suggest that youth should engage in both aerobic and muscle strengthening exercise to improve overall health (1). Indeed, randomized controlled studies in adults demonstrate that the combination of AE and RE is a better exercise strategy than either exercise

367 modality alone to improve glycemic control (7, 36) or insulin sensitivity (10). However, in
368 children and adolescents it is currently unknown whether a combined AE and RE program would
369 be associated with greater improvements in insulin sensitivity than either exercise alone and
370 whether the response would be similar in boys and girls. Further investigations should shed light
371 on this.

372 Limitations of this study warrant mention. Given the set length of intervention and the
373 acute effects of exercise on insulin sensitivity, we were unable to measure insulin sensitivity
374 during the same menstrual cycle before and after the intervention, which was true for all three
375 groups. Our findings are limited to obese healthy black and white adolescent girls. Whether our
376 findings would remain true in other racial groups, prepubertal girls and girls with oral or
377 injectable contraceptives or girls with type 2 diabetes are unknown. Although we randomly
378 assigned participants to intervention groups, this does not always result in similar characteristics
379 between groups. Indeed, at randomization subjects in the RE group tended to have higher %
380 body fat and lower insulin sensitivity compared with those in the AE group. As treatment
381 changes are often related to the baseline value (i.e. poorer baseline values allow for a potentially
382 larger improvement), we adjusted all analyses examining treatment effects for that corresponding
383 baseline value. However, due to the small sample size in this study, we did not simultaneously
384 adjust for all group baseline differences as this may limit our power and potentially be an over-
385 adjustment as many of the health and obesity markers are inter-correlated. Although,
386 participants were asked to log their energy intake during the study, this was completed by very
387 few participants, and was generally done poorly.

388 In summary, the results of this study suggest that in previously sedentary, obese
389 adolescent girls both aerobic and resistance exercise (3 days/weeks, ~180 min/week), without

calorie restriction and weight loss, is associated with reductions in total fat and IMAT. However, only aerobic exercise and not resistance exercise is associated with reductions in visceral adiposity and liver fat and improvement in insulin sensitivity, a major risk factor for type 2 diabetes in youth.

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The authors' contributions were as follows. Lee designed the study, obtained funding, researched data and wrote manuscript. Deldin, White and Kim trained research participants, analyzed MRI data and performed exercise testing. Libman, Rivera-Vega and Sandoval researched data and reviewed manuscript. Kuk performed statistical analyses and provided critical revision of the manuscript. Boesch assisted MRS data analyses and acquisition and reviewed manuscript. Arslanian provided funding, laboratory analyses and critical revision of the manuscript. Lee is the guarantor of this work, had full access to all the data and takes full responsibility for the integrity of data and the accuracy of data analysis.

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DISCLOSURES

All authors have no conflicts of interest to declare.

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618 **Table 1.** Subject characteristics at baseline
619

	Control *n* =12	Aerobic Exercise *n* = 16	Resistance Exercise *n* = 16	*P*	*P* §
Black/White (*n*)	9/3	9/7	12/4	0.438	
Puberty, III/IV/V (*n*)	0/1/11	0/3/13	0/2/14	0.719	
Anthropometric					
Age (years)	15.0 ± 2.2	14.6 ± 1.9	14.8 ± 1.9	0.819	
Body weight (kg)	93.3 ± 13.1	88.9 ± 16.3	97.1 ± 16.0	0.326	
BMI (kg/m^2)	35.3 ± 4.0	32.9 ± 3.8	36.4 ± 3.8 †	0.049	
Waist (cm)	110. 9 ± 8.4	106.5 ± 11.1	115.3 ± 11.7	0.079	
MRI *					
Total AT (kg)	48.1 ± 9.4	43.3 ± 11.0	50.4 ± 11.5	0.186	0.760
Total body fat (%)	51.3 ± 3.5	47.8 ± 4.2	51.5 ± 4.7 †	0.035	0.298
Skeletal muscle (kg)	22.7 ± 2.7	23.0 ± 4.2	23.2 ± 3.1	0.928	0.206
VAT (cm^2)	58.6 ± 23.7	51.8 ± 23.3	63.2 ± 23.6	0.407	0.576
ASAT (cm^2)	538.2 ± 117.9	444.5 ± 155.0	536.8 ± 127.9	0.114	0.545
Intrahepatic lipid (%)	3.0 ± 5.4	2.2 ± 3.3	2.0 ± 1.3	0.738	0.530
CT at mid-thigh					
IMAT (cm^2)	59.3 ± 13.3	53.8 ± 24.7	58.3 ± 18.9	0.736	0.376
Muscle attenuation (HU)	52.0 ± 1.6	52.2 ± 2.5	50.7 ± 3.4	0.231	0.526
Metabolic					
Fasting glucose (mg/dl)	97.0 ± 6.7	93.2 ± 5.9	94.4 ± 6.8	0.309	0.410
Fasting insulin (μU/ml)	31.1 ± 15.3	28.6 ± 16.5	45.8 ± 22.0 †	0.026	0.082
Fasting HGP (mg/kg/min)	1.89 ± 0.38	1.87 ± 0.29	1.79 ± 0.44	0.165	0.206
Fasting Hepatic insulin sensitivity (mg/kg/min per μU/ml^{-1})	22.9 ± 14.4	24.2 ± 12.2	16.5 ± 10.5	0.188	0.101
Glucose at 2 hr (mg/dl)	121.7 ± 28.5	120.7 ± 19.8	117.7 ± 15.5	0.865	0.797
Insulin at 2 hr (μU/ml)	104.1 ± 102.8	153.6 ± 143.7	207.0 ± 170.8	0.188	0.171
Glucose AUC (mg·min/dl)	15283.9 ± 3044.2	14818.1 ± 2363.7	14748.0 ±1334.9	0.807	0.564
Insulin AUC (μU·min/ml)	15781.8 ± 8121.4	17038.0 ± 14281.2	28605.9 ± 17643.8 ‡	0.035	0.077
Insulin sensitivity (mg/kg/min per μU/ml)	2.7 ± 1.3	2.8 ± 1.3	1.8 ± 0.8 †	0.034	0.101
Insulin sensitivity (mg/kgFFM/min per μU/ml)	5.1 ± 2.5	5.1 ± 2.4	3.4 ± 1.6	0.060	0.100
Fitness					
VO_{2peak} (ml/kg/min)	23.9 ± 3.0	28.5 ± 3.8	24.3 ± 4.3 †	0.004	0.090
Muscular strength index	1.0 ± 0.2	1.1 ± 0.2	1.0 ± 0.2	0.897	0.906

620 Values are means (SD). * *n*=15 in the aerobic group.
621† Different from the aerobic exercise group (*P*<0.05). ‡ Different from the control group (*P*=0.06).
622§ ANCOVA adjusting for BMI and race. AT, adipose tissue; VAT, visceral AT; ASAT, abdominal subcutaneous AT
623 IMAT, intermuscular AT; HGP, hepatic glucose production; AUC, area under the curve.

Table 2. Absolute changes in total and regional fat distribution and fitness after 3 months

	Control (*n*=8/ITT=12)	Aerobic Exercise (*n* =14/ITT =16)		Resistance Exercise (*n* =14/ITT =16)	
	Mean ± SE	Mean ± SE	*P*	Mean ± SE	*P*
		Intent-to-Treat Analysis (*n* = 44)			
Body weight (kg)	0.13 ± 1.10	-1.31 ± 1.43	0.360	-0.31 ± 1.38	0.822
BMI (kg/m^2)	-0.03 ± 0.44	-0.46 ± 0.58	0.430	-0.28 ± 0.54	0.608
Waist (cm)	-0.25 ± 1.30	-2.48 ± 1.67	0.137	-1.82 ± 1.66	0.271
Total AT (kg)	0.70 ± 1.01	-2.38 ± 1.25	0.058	-2.23 ± 1.21	0.065
Total body fat (%)	0.10 ± 0.66	-1.70 ± 0.85	0.046	-1.63 ± 0.78	0.035
Skeletal muscle (kg)	0.21 ± 0.51	0.13 ± 0.63	0.834	0.61 ± 0.61	0.317
VAT (cm^2)	5.87 ± 6.17	-15.68 ± 7.64	0.041	-4.52 ± 7.23	0.532
ASAT (cm^2)	-2.93 ± 16.3	-7.78 ± 20.42	0.703	-14.36 ± 19.61	0.464
Intrahepatic lipid (%)	0.75 ± 0.57	-1.70 ± 0.74	0.022	-0.70 ± 0.69	0.308
IMAT (cm^2)	1.1 ± 3.4	-13.5 ± 4.2	0.001	-10.9 ± 4.2	0.010
Muscle attenuation (HU)	0.41 ± 0.42	0.13 ± 0.53	0.811	0.23 ± 0.54	0.678
VO_{2peak} (ml/kg/min)	-0.21 ± 1.42	4.91 ± 1.82	0.007	2.87 ± 1.71	0.095
Muscular strength index	0.07 ± 0.09	0.08 ± 0.11	0.481	0.45 ± 0.11	<0.0001
		Per-Protocol Analysis (*n* = 36)			
Body weight (kg)	0.28 ± 1.1	-1.44 ± 0.84	0.307	-0.44 ± 0.83	0.748
BMI (kg/m^2)	0.02 ± 0.44	-0.52 ± 0.57	0.369	-0.34 ± 0.54	0.540
Waist (cm)	-0.37 ± 1.22	-2.39 ± 1.56	0.135	-1.72 ± 1.57	0.281
Total AT (kg)	0.67 ± 0.96	-2.33 ± 1.21	0.063	-2.20 ± 1.18	0.072
Total body fat (%)	0.08 ± 0.63	-1.66 ± 0.81	0.050	-1.61 ± 0.76	0.041
Skeletal muscle (kg)	0.20 ± 0.49	0.16 ± 0.61	0.798	0.63 ± 0.60	0.297
VAT (cm^2)	4.91 ± 5.79	-15.40 ± 7.29	0.043	-4.28 ± 7.03	0.547
ASAT (cm^2)	-3.2 ± 15.70	-6.92 ± 19.77	0.729	-13.69 ± 19.14	0.480
Intrahepatic lipid (%)	0.55 ± 0.56	-1.59 ± 0.70	0.031	-0.59 ± 0.69	0.398
IMAT (cm^2)	0.8 ± 3.3	-13.3 ± 4.13	0.003	-10.9 ± 4.2	0.014
Muscle attenuation (HU)	0.39 ± 0.42	0.15 ± 0.52	0.766	0.22 ± 0.53	0.682
VO_{2peak} (ml/kg/min)	-0.43 ± 1.36	5.17 ± 1.78	0.007	3.10 ± 1.69	0.077
Muscular strength index	0.07 ± 0.09	0.08 ± 0.11	0.459	0.45 ± 0.11	0.0003

Values are imputed means (SE).
Change values for the intervention groups are the difference as compared to control with adjustment for baseline values as assessing using ANCOVA.
P-values as compared to the control group.
ITT, Intent-to-treat; AT, adipose tissue; VAT, visceral AT; ASAT, abdominal subcutaneous AT; IMAT, intermuscular AT; HU, Hounsfield unit.

632 **Table 3.** Absolute changes in metabolic variables after 3 months

	Control (*n*=8/ITT=12)	Aerobic Exercise (*n* =14/ITT =16)		Resistance Exercise (*n* =14/ITT =16)	
	Mean ± SE	Mean ± SE	*P*	Mean ± SE	*P*
		Intent-to-Treat Analysis (*n* = 44)			
Fasting glucose (mg/dl)	1.35 ± 2.03	-2.11 ± 2.64	0.424	0.61 ± 2.54	0.811
Fasting insulin (μU/ml)	0.07 ± 3.34	-7.62 ± 4.33	0.079	-1.29 ± 4.37	0.768
Fasting HGP (mg/kg/min)	-0.09 ± 0.16	0.32 ± 0.20	0.120	0.14 ± 0.20	0.491
Hepatic insulin sensitivity (mg/kg/min per μU/ml^{-1})	0.87 ± 3.17	-0.04 ± 4.11	0.992	-6.96 ± 3.97	0.080
Glucose at 2 hr (mg/dl)	5.47 ± 6.39	-3.01 ± 8.0	0.706	-2.01 ± 8.12	0.805
Insulin at 2 hr (μU/ml)	15.17 ± 39.48	-60.66 ± 49.62	0.222	9.25 ± 50.53	0.855
Glucose AUC (mg·min/dl)	12.95 ± 490.55	62.69 ± 630.72	0.921	-126.12 ± 613.69	0.837
Insulin AUC (μU·min/ml)	-837.00 ± 2927.61	-4087.57 ± 3715.96	0.272	-2441.82 ± 3834.03	0.524
Insulin sensitivity (mg/kg/min per μU/ml)	-0.46 ± 0.21	0.92 ± 0.27	0.0007	0.03 ± 0.27	0.902
Insulin sensitivity (mg/kgFFM/min per μU/ml)	-0.79 ± 0.35	1.43 ± 0.44	0.0011	-0.13 ± 0.45	0.767
		Per-Protocol Analysis (*n* = 36)			
Fasting glucose (mg/dl)	1.60 ± 2.01	-2.35 ± 2.53	0.361	0.38± 2.52	0.882
Fasting insulin (μU/ml)	-0.05 ± 3.34	-8.03 ± 4.19	0.064	-1.65 ± 4.3	0.707
Fasting HGP (mg/kg/min)	-0.09 ± 0.156	2.92 ± 0.20	0.146	0.12 ± 1.96	0.556
Hepatic insulin sensitivity (mg/kg/min per μU/ml^{-1})	1.39 ± 3.12	-0.25 ± 3.96	0.951	-7.22 ± 3.95	0.077
Glucose at 2 hr (mg/dl)	4.74 ± 6.24	-2.56 ± 7.80	0.745	-2.00 ± 7.97	0.803
Insulin at 2 hr (μU/ml)	10.8 ± 38.8	-57.70 ± 48.42	0.242	9.49 ± 49.74	0.850
Glucose AUC (mg·min/dl)	43.44 ± 485.72	7.47 ± 608.45	0.990	-180.29 ± 609.69	0.769
Insulin AUC (μU·min/ml)	-739.76 ± 2921.24	-4418.58 ± 3590.20	0.227	-2764.87 ± 3820.03	0.475
Insulin sensitivity (mg/kg/min per μU/ml)	-0.49 ± 0.21	1.10 ± 0.07	0.0002	0.07 ± 0.26	0.793
Insulin sensitivity (mg/kgFFM/min per μU/ml)	-0.78 ± 0.34	1.44 ± 0.43	0.0021	-0.13 ± 0.44	0.778

633 Values are imputed means (SE).
634 Change values for the intervention groups are the difference as compared to control with adjustment for baseline
635 values as assessing using ANCOVA.
636 *P*-values as compared to the control group.
637 HGP: hepatic glucose production
638

FIGURE LEGENDS

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

FIGURE 2. Absolute change in hepatic insulin sensitivity and peripheral insulin sensitivity for each intervention group. Values for the control group are imputed means (SE). Change values for the intervention groups are the difference as compared to control with adjustment for baseline values as assessing using ANCOVA. * $P<0.001$ as compared to the control group.

Figure 1

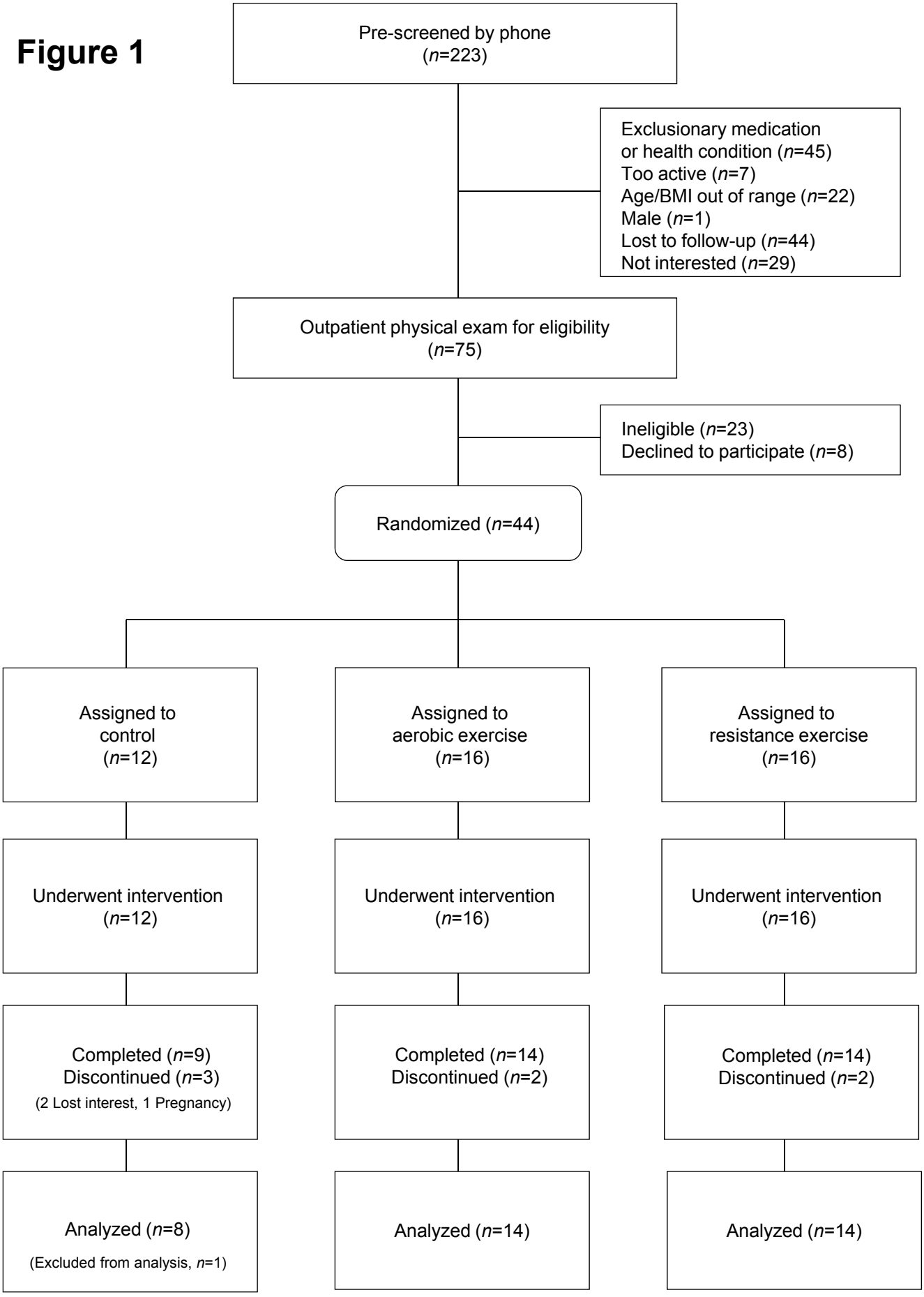
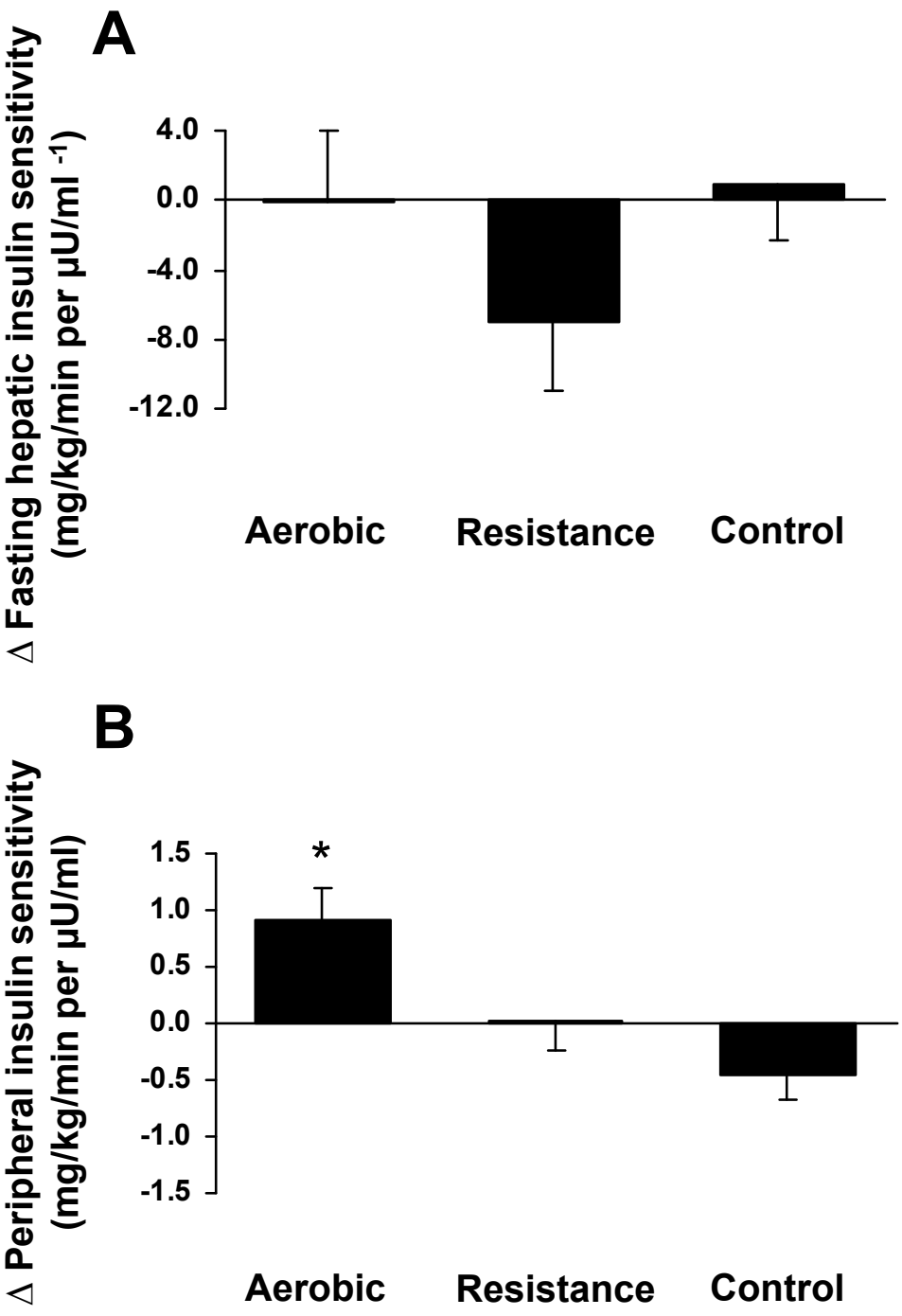

Pre-screened by phone
(n=223)
Exclusionary medication
or health condition (n=45)
Too active (n=7)
Age/BMI out of range (n=22)
Male (n=1)
Lost to follow-up (n=44)
Not interested (n=29)
Outpatient physical exam for eligibility
(n=75)
Ineligible (n=23)
Declined to participate (n=8)
Randomized (n=44)
Assigned to
control
(n=12)
Assigned to
aerobic exercise
(n=16)
Assigned to
resistance exercise
(n=16)
Underwent intervention
(n=12)
Underwent intervention
(n=16)
Underwent intervention
(n=16)
Completed (n=9)
Discontinued (n=3)
(2 Lost interest, 1 Pregnancy)
Completed (n=14)
Discontinued (n=2)
Completed (n=14)
Discontinued (n=2)
Analyzed (n=8)
(Excluded from analysis, n=1)
Analyzed (n=14)
Analyzed (n=14)

Figure 2


A
Δ Fasting hepatic insulin sensitivity (mg/kg/min per μU/ml -1)
4.0
0.0
-4.0
-8.0
-12.0
Aerobic
Resistance
Control
B
Δ Peripheral insulin sensitivity (mg/kg/min per μU/ml)
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
*
Aerobic
Resistance
Control