Research Square

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Changes in Metabolic, Inflammatory, and Vascular Markers During a 4-Week Residential Exercise and Dietary Intervention in Adolescents With Obesity: An Exploratory Pre-Post Study

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Research Article

Keywords: adolescents with obesity, lifestyle intervention, leptin-to-adiponectin ratio, vascular endothelium

Posted Date: November 1st, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10895839/v1

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Additional Declarations: No competing interests reported.

Abstract

Objective

To investigate the effects of a 4-week intensive lifestyle intervention on anthropometric measures, glucose and lipid metabolism, and vasomotor homeostasis in adolescents with obesity. We also examined heterogeneity in metabolic responses and mechanisms of endothelial adaptation according to the baseline leptin-to-adiponectin ratio (L/A ratio).

Methods

Forty adolescents with obesity completed a 4-week residential exercise and dietary intervention comprising regular aerobic exercise and dietary control. Anthropometric measures, glucose and lipid metabolism, serum inflammatory factors, and vascular endothelial markers were assessed before and after the intervention. Participants were stratified into high- and low-risk groups according to baseline L/A ratio. Partial correlation analyses controlled for confounders and examined associations between endocrine remodeling and endothelial repair.

Results

(1) After 4 weeks, body weight, body mass index (BMI), body fat percentage, and measures of central adiposity decreased significantly. Circulating nitric oxide (NO) increased significantly, endothelin-1 (ET-1) decreased, and the nitric oxide/endothelin-1 ratio (NO/ET-1 ratio) increased markedly. (2) Despite comparable reductions in body composition, metabolic improvement was significantly greater in the high-risk group than in the low-risk group. Specifically, the high-risk group showed greater improvement in the homeostatic model assessment for insulin resistance (HOMA-IR), greater triglyceride clearance, and a larger reduction in tumor necrosis factor alpha (TNF-α). (3) After adjustment for age, sex, and baseline BMI, changes in the L/A ratio remained positively correlated with changes in TNF-α. Changes in high-sensitivity C-reactive protein (hs-CRP) were negatively correlated with changes in von Willebrand factor (vWF). The biochemical clearance of hs-CRP appeared to precede the mechanical remodeling of the vascular endothelium reflected by vWF, indicating a temporal lag in short-term adaptation.

Conclusion

The L/A ratio can serve as a biomarker for cardiometabolic risk stratification in adolescents with obesity. Beyond broadly improving anthropometric outcomes, the intensive lifestyle intervention may preferentially promote deeper metabolic remodeling and recovery of endothelial function in high-risk individuals.

Trial registration:

The study was approved by the Scientific Research Ethics Committee of Shanghai University of Sport (Approval No. 102772024RT158)

Introduction

In recent years, the prevalence of overweight and obesity among children and adolescents in China has continued to rise. China now has the world's largest affected population, and its disease burden is rapidly approaching that of developed countries [1, 2]. Clinical and epidemiological evidence indicates that childhood obesity directly impairs

cardiovascular, respiratory, and endocrine function. It also substantially increases the risk of cardiovascular disease, type 2 diabetes, and other chronic diseases in adulthood [3]. Pathophysiologically, obesity is often accompanied by dyslipidemia and insulin resistance in peripheral tissues. Excess visceral adipose tissue acts as a dysfunctional endocrine and immune organ. It markedly increases the release of tumor necrosis factor alpha (TNF-α), high-sensitivity C-reactive protein (hs-CRP), and other proinflammatory factors, sustaining chronic low-grade inflammation [4]. If unchecked, persistent inflammation and oxidative stress further injure vascular endothelial cells, increase intercellular adhesion molecule expression, and accelerate the pathological progression of atherosclerosis [5, 6].

Despite these concerns, current intervention research and clinical translation for adolescents with obesity have two important limitations. First, stratified studies based on endocrine markers remain scarce. Most intervention studies rely on routine pre-post comparisons of macroscopic anthropometric measures and overlook pronounced individual heterogeneity in the severity of metabolic dysfunction. Second, the temporal relationship between vascular endothelial repair and the resolution of inflammation remains unclear.

Given marked individual differences in clinical metabolic and cardiovascular risk factors, we analyzed data from 40 adolescents with obesity. All participants attended a residential exercise and weight-loss summer camp, and stratified analyses were used to characterize metabolic differences among subtypes. Our group's extensive experience with residential exercise and weight-loss programs has generated several relevant findings. Four weeks of residential aerobic exercise can reduce body weight, body fat percentage, and body circumferences, thereby improving anthropometric status. It can also restore glucose and lipid metabolic balance and reduce serum proinflammatory factors [7]. Previous work further showed improvements in vascular endothelial function and visceral fat deposition [8], with corresponding benefits for cardiovascular and overall health.

Building on this work, the present study further examined individual metabolic heterogeneity during the exercise intervention. We tracked conventional body-composition and glucose and lipid metabolic indices over 4 weeks. We also introduced the baseline L/A ratio for molecular stratification and compared metabolic benefits between risk subtypes with comparable fat loss. Finally, partial correlation models explored a potential temporal lag between acute inflammation resolution, indexed by hs-CRP, and vascular endothelial activation, indexed by vWF.

Materials and Methods

1.1 Participants

Participants were adolescents with obesity aged 11–15 years who attended a weight-loss summer camp operated by Shanghai Dianfeng Health Technology Co., Ltd. The study was approved by the Scientific Research Ethics Committee of Shanghai University of Sport (Approval No. 102772024RT158). The present study was an exploratory secondary analysis of data from the originally approved research project. The participants, exercise and dietary intervention, sample collection, and measurements of glucose and lipid metabolism were all within the original approved protocol. All participants and their legal guardians signed informed consent forms before the study began. This secondary analysis introduced no new intervention, sample collection, or risk to participants.

The study included 40 participants, comprising 20 male and 20 female participants. Additional inclusion criteria were as follows. (1) Before admission, participants completed a general medical examination and a laboratory-based graded exercise test to exclude possible cardiovascular disease. (2) Participants did not smoke and had not taken weight-loss medication during the preceding six months. (3) Participants had no renal or endocrine disease. (4) Participants did not regularly engage in physical exercise. (5) Participants and their guardians were informed about and consented to the study. General participant characteristics are presented in Table 1.

Table 1
Baseline characteristics of adolescents with obesity (N = 40)

Variable	Summary statistic	Baseline value	Unit
Age	Mean ± SD	13.42 ± 2.04	years
Body weight	Mean ± SD	75.52 ± 17.26	kg
BMI	Mean ± SD	29.02 ± 3.95	kg/m²
Body fat percentage	Mean ± SD	38.21 ± 7.16	%
PAI-1	Median (IQR)	24.88 (15.56, 36.00)	ng/mL
sICAM-1	Median (IQR)	445.93 (384.95, 479.63)	ng/mL
vWF	Median (IQR)	1339.78 (1142.21, 1489.00)	ng/mL
NO	Median (IQR)	32.37 (23.02, 47.84)	μmol/L
ET-1	Median (IQR)	18.61 (9.63, 29.81)	pg/mL
sTNFR2	Median (IQR)	20.91 (17.65, 25.80)	ng/mL
IL-6	Median (IQR)	193.42 (111.08, 348.83)	pg/mL
TNF-α	Median (IQR)	83.67 (50.61, 124.30)	pg/mL
hs-CRP	Median (IQR)	1.73 (1.09, 4.09)	mg/L
Adiponectin	Median (IQR)	1.04 (0.71, 1.52)	μg/mL
Leptin	Median (IQR)	4.62 (3.38, 5.73)	ng/mL

1.2 Study Methods

1.2.1 Intervention Protocol

Participants were managed in a fully residential setting throughout the intervention. The exercise protocol comprised the following components.

1. Participants completed a 4-week program of low- to moderate-intensity aerobic exercise.
2. Exercise intensity was monitored using heart rate. The target intensity was 60%-80% heart rate reserve (HRR), calculated as follows: target heart rate = (220 - age - resting heart rate) × 60%-80% + resting heart rate. Polar heart rate monitors were used for real-time telemetry, and exercise intensity was adjusted as needed.
3. Participants exercised six days per week, with one 1.5-hour session each morning and afternoon.
4. Each exercise session began with 15–20 minutes of preparatory activity to prevent injury. Participants completed 10–15 minutes of cool-down activity after exercise to facilitate recovery.
5. Activities primarily included simple ball games, walking in water, and aerobic fitness exercises, combined with jogging, cycle ergometry, and elliptical training.
6. Exercise-intensity supervisors, coaches, and exercise medical supervisors had relevant professional backgrounds. All completed the company's standardized training program.

A professional dietitian provided individualized meals based on resting metabolic rate. The amount of staple food was allocated according to body weight, while all participants received the same dishes. The energy ratio across breakfast, lunch, and dinner was 3:4:3. Dietary fiber was increased to prevent constipation, and vitamin and mineral intake was

increased to maintain physiological homeostasis after exercise. Participants were prohibited from consuming snacks to ensure the effectiveness of the intervention.

1.2.2 Outcome Measures and Methods

1) Anthropometric measures. Height, weight, and body fat percentage (FAT%) were measured using a TANITA TBF-418B body fat analyzer. Waist circumference (WC) and hip circumference (HC) were measured using a flexible measuring tape. All measurements were performed by specially trained assessors.

2) Blood pressure and heart rate. Heart rate and blood pressure were measured using an X64057.7 blood pressure and pulse monitor manufactured in Japan. Participants first rested quietly in a seated position for 5–10 minutes. Three measurements were obtained and averaged, and systolic blood pressure, diastolic blood pressure, and heart rate were recorded.

3) Blood measures. In the morning after fasting, 3 mL of venous blood was collected from each participant, and serum was separated for analysis. Triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) were measured by an oxidase method using a fully automated biochemical analyzer. Fasting plasma glucose (FPG) was measured by the glucose oxidase method, and fasting insulin (FINS) was measured by radioimmunoassay.

4) Derived measures. The derived measures were waist-to-hip ratio (WHR) = waist circumference/hip circumference, the leptin-to-adiponectin ratio (L/A ratio), homeostatic model assessment for insulin resistance (HOMA-IR), and the nitric oxide/endothelin-1 ratio (NO/ET-1 ratio). HOMA-IR, the L/A ratio, and the NO/ET-1 ratio were calculated before statistical analysis for both pre-intervention and post-intervention data. HOMA-IR was calculated as (FPG × FINS)/22.5, with FPG expressed in mmol/L and FINS in μU/mL. The L/A ratio was calculated by dividing serum leptin concentration by serum adiponectin concentration, measured in ng/mL and μg/mL, respectively. The NO/ET-1 ratio was calculated by dividing serum NO concentration by serum ET-1 concentration. NO and ET-1 were measured in μmol/L and pg/mL, respectively. The two ratios were therefore calculated using the stated assay-unit conventions. The same calculation rules were applied to pre-intervention and post-intervention measurements, and missing values were not imputed.

All measures were assessed once before admission and again after one day of rest following completion of the exercise intervention.

1.2.3 Statistical Analysis

The Shapiro-Wilk test was used to assess the normality of all continuous variables.

1. Anthropometric variables, such as height, weight, and BMI, were normally distributed and are reported as mean ± standard deviation (Mean ± SD). Pre-intervention and post-intervention values were compared using paired-samples t tests.
2. Adipokines and vascular inflammatory markers, including leptin, adiponectin, hs-CRP, and RBP4, showed substantial interindividual variation and non-normal distributions ($P < 0.05$). These data are reported as the median and interquartile range [Median (Q1, Q3)]. Pre-intervention and post-intervention values were compared using the nonparametric Wilcoxon signed-rank test. Statistical significance was defined as $P < 0.05$ for all analyses.

Results

2.1 Overall intervention effects

Table 2
Effects of the 4-week residential exercise and dietary intervention on anthropometric measures in adolescents with obesity

Anthropometric measure	Unit	Pre-intervention, mean ± SD	Post-intervention, mean ± SD	t statistic	P value
Body weight	kg	75.52 ± 17.09	69.04 ± 15.69	20.768	< 0.001
BMI	kg/m²	29.02 ± 3.88	26.41 ± 3.53	23.971	< 0.001
Body fat percentage	%	38.21 ± 7.26	32.29 ± 6.69	14.134	< 0.001

Table 2 shows that the main anthropometric measures decreased significantly after the 4-week residential exercise and dietary intervention. Body weight decreased from 75.52 ± 17.09 kg before the intervention to 69.04 ± 15.69 kg after the intervention ($P < 0.001$). BMI decreased from 29.02 ± 3.88 kg/m² to 26.41 ± 3.53 kg/m² ($P < 0.001$). Body fat percentage also decreased from 38.21 ± 7.26% to 32.29 ± 6.69% ($P < 0.001$).

Table 3
Effects of the 4-week residential exercise and dietary intervention on metabolic, inflammatory, and vascular homeostasis measures in adolescents with obesity

Measure	Unit or scale	n	Pre-intervention, median (Q1, Q3)	Post-intervention, median (Q1, Q3)	W statistic	P value
Leptin-to-adiponectin ratio (L/A ratio)	Scale-dependent ratio	40	4.53 (2.91, 6.42)	0.73 (0.30, 1.16)	0.00	< 0.001
HOMA-IR	Index	40	4.03 (2.83, 5.38)	1.49 (1.15, 1.89)	0.00	< 0.001
NO/ET-1 ratio	Scale-dependent ratio	40	2.06 (1.10, 3.84)	7.77 (4.02, 11.05)	98.00	< 0.001
Triglycerides (TG)	mmol/L	40	1.35 (0.96, 2.11)	0.68 (0.55, 0.77)	11.50	< 0.001
Low-density lipoprotein cholesterol (LDL-C)	mmol/L	40	2.94 (2.27, 3.26)	1.98 (1.79, 2.36)	4.00	< 0.001
High-sensitivity C-reactive protein (hs-CRP)	mg/L	40	1.76 (1.10, 4.06)	0.13 (0.00, 0.36)	64.00	< 0.001
Tumor necrosis factor alpha (TNF-α)	pg/mL	40	84.35 (51.25, 130.82)	112.13 (64.28, 183.73)	228.00	0.063

Table 3 shows that HOMA-IR and the leptin-to-adiponectin ratio (L/A ratio) decreased significantly after the intervention ($P < 0.001$). Triglycerides and LDL-C also decreased significantly from their pre-intervention levels ($P < 0.001$).

For inflammatory and vascular homeostasis markers, median hs-CRP decreased significantly from 1.76 before the intervention to 0.13 afterward ($P < 0.001$). Overall TNF-α tended to increase, but the difference between pre-intervention and post-intervention values was not statistically significant ($P = 0.063$). The NO/ET-1 ratio also increased significantly after the intervention ($P < 0.001$), indicating improved vasodilation and endothelial homeostasis.

2.2 Subgroup analysis based on baseline L/A ratio

To examine whether baseline adipose endocrine imbalance was associated with heterogeneity in the response, we conducted an exploratory subgroup analysis. Participants were divided at the cohort median baseline L/A ratio of 4.64. The high-risk group (L/A ratio > 4.64) comprised 20 participants, and the low-risk group (L/A ratio < 4.64) comprised 20 participants.

Table 4
Changes in anthropometric and body-composition measures by baseline metabolic risk group

Change score (Δ)	Unit	Low-risk group (n = 20), mean ± SD	High-risk group (n = 20), mean ± SD	t statistic	P value
Δ body weight	kg	-6.37 ± 2.19	-6.62 ± 10.54	-0.11	0.911
Δ BMI	kg/m²	-2.62 ± 0.71	-2.67 ± 1.66	-0.14	0.888
Δ body fat percentage	%	-6.52 ± 2.78	-5.97 ± 2.78	0.64	0.526
Δ waist circumference	cm	-13.20 ± 4.02	-12.42 ± 4.88	0.56	0.576
Δ hip circumference	cm	-9.50 ± 2.26	-9.17 ± 5.91	0.25	0.805
Δ upper-arm skinfold	mm	-5.69 ± 1.79	-4.98 ± 3.93	0.79	0.436
Δ subscapular skinfold	mm	-8.06 ± 3.85	-6.40 ± 3.65	1.39	0.173

As shown in Table 4, participants were classified as the high-risk group (n = 20) or low-risk group (n = 20) using the median baseline L/A ratio (4.64). Independent-samples t tests showed no significant between-group differences in anthropometric or body-composition improvements after the 4-week intervention (all P > 0.05).

Changes were highly consistent between groups for body weight (high-risk vs. low-risk: Δ body weight, -6.62 ± 10.54 kg vs. -6.37 ± 2.19 kg; P = 0.911) and BMI (ΔBMI, -2.67 ± 1.66 kg/m² vs. -2.62 ± 0.71 kg/m²; P = 0.888). Body fat percentage changed by -5.97 ± 2.78% in the high-risk group and − 6.52 ± 2.78% in the low-risk group (P = 0.526). Reductions in waist and hip circumferences and subcutaneous fat thickness also followed similar, parallel patterns in both groups.

Table 5
Between-group comparison of intervention-related changes by baseline metabolic risk group

Change score (Δ)	Unit or scale	Low-risk group (n = 20), median (Q1, Q3)	High-risk group (n = 20), median (Q1, Q3)	U statistic	P value
ΔL/A ratio	Scale-dependent ratio	-2.48 (-3.20, -1.84)	-5.92 (-8.89, -4.57)	4.0	< 0.001
ΔHOMA-IR	Index	-2.45 (-3.06, -0.97)	-3.13 (-5.31, -2.20)	119.0	0.048
ΔNO/ET-1 ratio	Scale-dependent ratio	+ 3.10 (0.87, 5.94)	+ 5.65 (2.60, 7.46)	196.0	0.258
ΔTG	mmol/L	-0.53 (-0.85, -0.13)	-1.18 (-1.78, -0.45)	110.0	0.025
ΔTNF-α	pg/mL	+ 50.23 (2.23, 111.00)	-9.89 (-30.99, 19.34)	91.0	0.006
Δhs-CRP	mg/L	-1.04 (-3.66, -0.18)	-1.68 (-3.75, -1.33)	136.0	0.133

The groups achieved similar weight loss, but the magnitudes of improvement in metabolic and inflammatory markers differed significantly (Table 5). Mann-Whitney U tests for independent samples indicated greater benefits across several

molecular targets in the high-risk group than in the low-risk group.

For glucose and lipid metabolism and endocrine function, the L/A ratio decreased significantly more in the high-risk group than in the low-risk group (median, -5.92 vs. -2.48; $P < 0.001$). The high-risk group also showed greater TG clearance (ΔTG, -1.18 mmol/L vs. -0.53 mmol/L; $P = 0.025$). Its improvement in HOMA-IR was also significantly greater (ΔHOMA-IR, -3.13 vs. -2.45; $P = 0.048$).

For systemic inflammation, the between-group difference was reflected in changes in TNF-α. After the intervention, the low-risk group showed a compensatory slight increase in TNF-α (median, + 50.23). In contrast, the high-risk group showed a decrease in inflammation (median, -9.89), with a highly significant between-group difference ($P = 0.006$). The intervention-induced change in the NO/ET-1 ratio did not differ significantly between groups ($P = 0.258$). However, the median increase was greater in the high-risk group (+ 5.65) than in the low-risk group (+ 3.10).

2.3 Correlations related to pathophysiological mechanisms

To examine potential pathways underlying metabolic improvements, we analyzed intervention-induced changes (Δ) in key measures using Spearman rank correlations. These measures covered anthropometry, glucose and lipid metabolism, adipokines, and vascular inflammation.

Scatterplot regression showed a significant positive correlation between ΔBMI and ΔTG ($r = 0.408$, $P = 0.012$; Fig. 1). The magnitude of the intervention-associated decrease in BMI was significantly concordant with the magnitude of improvement in lipid metabolism.

Analysis of adipose endocrine function and systemic inflammation showed a significant positive correlation between ΔL/A ratio and ΔTNF-α ($r = 0.377$, $P = 0.023$; Fig. 2). This pattern indicated a close statistical association between decreases in the L/A ratio and simultaneous decreases in TNF-α.

Analysis of systemic low-grade inflammation and endothelial function showed that Δhs-CRP correlated negatively with ΔvWF, an endothelial injury and shedding marker ($r = -0.362$, $P = 0.030$; Fig. 3). During the 4-week intervention, decreases in acute inflammatory markers were inversely associated with changes in circulating endothelial marker levels.

Marked individual heterogeneity in age, sex-related development, and baseline body weight was present among adolescents with obesity. To reduce potential confounding by these baseline differences, we conducted multivariable-adjusted Spearman partial rank correlation analyses (Table 6). The associations between changes in metabolic and endothelial markers persisted after controlling for age, sex, and baseline BMI.

After accounting for baseline body weight and age, ΔL/A ratio remained significantly and independently positively correlated with the reduction in TNF-α. This finding indicated that intervention-related clearance of systemic low-grade inflammation was associated with an improved adipocyte paracrine microenvironment. Similarly, the negative association between Δhs-CRP and ΔvWF remained significant after covariate adjustment.

Table 6
Spearman partial rank correlations of changes (Δ) in core physiological and endothelial markers before and after adjustment for baseline covariates (N = 40)

Analysis domain	Variable X	Variable Y	Controlled covariates	Zero-order correlation (r)	Partial correlation (r_partial)	t statistic	P value	Significance
Adipose endocrine and inflammation axis	ΔL/A ratio	ΔTNF-α (pg/mL)	Age, sex, baseline BMI	0.377	0.354	2.316	0.031	*
Systemic inflammation and endothelial remodeling axis	Δhs-CRP (mg/L)	ΔvWF (ng/mL)	Age, sex, baseline BMI	-0.362	-0.342	-2.228	0.038	*

Note

Δdenotes the change in each measure over the 4-week residential exercise and dietary intervention (post-intervention value minus pre-intervention value). The zero-order correlation coefficient is the unadjusted Spearman rank correlation coefficient. The partial correlation coefficient is the Spearman partial rank correlation coefficient adjusted for chronological age, sex, and baseline BMI. $P < 0.05$ indicates statistical significance.

Discussion

3.1 Improvements in Anthropometric Measures and Body Composition and Mobilization of Visceral Fat

The results showed marked improvements in anthropometric measures and body composition among the 40 adolescents with obesity after 4 weeks of aerobic exercise combined with dietary control. Across the full sample, mean body weight decreased by 6.48 kg, BMI by 2.65 kg/m², and body fat percentage by 6.23% by the end of the intervention (all $P < 0.001$). These findings are broadly consistent with recent clinical weight-loss studies in adolescents [9, 10]. Under a moderate-intensity exercise prescription monitored at 60%-80% of heart rate reserve and individualized energy control, participants maintained a stable negative energy balance that may have promoted the use of peripheral adipose tissue as an energy source.

Subgroup comparisons based on the median baseline L/A ratio showed no significant differences between the high-risk group (L/A ratio > 4.64) and low-risk group in reductions in body weight (-6.62 kg vs. -6.37 kg), BMI (-2.67 kg/m² vs. -2.62 kg/m²), or body fat percentage (-5.97% vs. -6.52%; all $P > 0.5$). These findings suggest that a moderate negative energy balance may improve anthropometric outcomes across metabolic-risk subgroups. Over a short intervention period, the rate of overall fat loss may not be strongly constrained by the initial severity of endocrine dysfunction [8].

However, reductions in body weight and total body fat do not fully explain the rapid improvements in lipid metabolism and insulin sensitivity. Exercise may mobilize adipose tissue differently across anatomical regions. Visceral adipocytes have a relatively high density of β-adrenergic receptors and a high glucocorticoid receptor content. Visceral fat may therefore show greater lipolytic activity than subcutaneous fat in response to exercise-induced catecholamine stimulation [11]. In the present study, waist circumference, an indicator of central obesity and visceral adiposity, decreased markedly in both groups. The reductions were 12.42 cm in the high-risk group and 13.20 cm in the low-risk

group. Previous evidence also suggests that visceral fat and ectopic lipid deposits in peripheral organs are preferentially mobilized during the early phase of negative energy balance [11].

Preferential mobilization of visceral fat provides an anatomical basis for the decrease in serum triglycerides (TG). The regression analysis showed a significant positive correlation between changes in BMI and TG ($r = 0.408$, $P = 0.012$; Fig. 1). The visceral fat depot is directly connected to the liver through the portal circulation. In severe obesity, sustained lipolysis of excess visceral fat delivers large amounts of free fatty acids to the liver through the portal vein. This process contributes to increased very-low-density lipoprotein synthesis and hypertriglyceridemia [9, 12].

The association between reductions in body size and circulating lipids in Fig. 1 suggests that the 4-week intervention reduced central adiposity and visceral fat accumulation. This anatomical change may have reduced free-fatty-acid delivery to the liver and the lipotoxic burden on peripheral target organs [9]. Improved body composition and mobilization of abdominal ectopic lipids may have contributed directly to triglyceride control. These changes may also have created favorable conditions for restoring peripheral insulin sensitivity and establishing a less inflammatory microenvironment.

3.2 Improvements in Glucose and Lipid Metabolism and Restoration of Insulin Sensitivity

As body composition and abdominal obesity improved, indices of glucose and lipid metabolism also changed favorably. At the end of the intervention, fasting plasma glucose (FPG), fasting insulin (FINS), and HOMA-IR were significantly lower across the full sample. TG and LDL-C also decreased (all $P < 0.001$). These findings are broadly consistent with recent network meta-analyses of interventions for childhood and adolescent obesity [13, 14]. Regular aerobic exercise increases ATP consumption in skeletal muscle and raises the intracellular AMP-to-ATP ratio, thereby activating AMP-activated protein kinase (AMPK) signaling [15]. This pathway can promote translocation of glucose transporter 4 to the sarcolemma independently of insulin-receptor signaling. The resulting increase in muscular glucose uptake may reduce the secretory burden on pancreatic β-cells and help alleviate hyperinsulinemia [13, 15].

Further subgroup analysis indicated that participants achieved similar reductions in body composition but differed in the magnitude of improvement in insulin sensitivity. The high-risk group at baseline (L/A ratio > 4.64) tended to show greater reductions in FINS and HOMA-IR than the low-risk group. Recent clinical studies have suggested that the L/A ratio may be more sensitive to adipose-tissue dysfunction and peripheral insulin resistance than leptin or adiponectin alone [16, 17]. A high baseline L/A ratio commonly indicates adipocyte hypertrophy and local secretory dysfunction.

Differences in the magnitude of improvement between the groups may reflect coordinated adaptation of adipose paracrine function and skeletal-muscle metabolism. Regular aerobic exercise combined with energy restriction may decrease leptin and increase adiponectin, thereby improving the circulating L/A ratio [14, 17]. Increased adiponectin can bind to adiponectin receptor 1 on skeletal-muscle cells and activate AMPK and peroxisome proliferator-activated receptor alpha pathways. These responses may accelerate free-fatty-acid β-oxidation [9] and reduce ectopic accumulation of lipotoxic products, including ceramides and diacylglycerols, within skeletal muscle.

Excess accumulation of ceramides and diacylglycerols can activate protein kinase C and promote serine/threonine phosphorylation of insulin receptor substrate 1. This abnormal phosphorylation inhibits canonical phosphoinositide 3-kinase/protein kinase B insulin signaling [9, 15]. In children with more severe baseline secretory imbalance and insulin resistance (L/A ratio > 4.64), the 4-week intervention may have acted through more than weight reduction. By improving the L/A ratio and promoting clearance of intramuscular lipids, it may have reduced inhibitory phosphorylation of insulin receptor substrate 1 and supported recovery of the phosphoinositide 3-kinase/protein kinase B pathway [14, 15].

3.3 Changes in Inflammatory Factors and Paracrine Regulation

As insulin sensitivity improved and peripheral lipotoxic stress decreased, systemic chronic low-grade inflammation also improved. After 4 weeks of aerobic exercise combined with dietary control, serum TNF-α increased slightly, whereas hs-CRP decreased significantly ($P < 0.001$). The serum L/A ratio, which reflects adipose paracrine function, also improved markedly. These endocrine and immune changes were broadly consistent with recent randomized trials and meta-analyses of exercise interventions in adolescents with obesity [13, 14, 17, 18].

Exercise-related anti-inflammatory effects are commonly attributed to reductions in body weight or total body fat. In the present multivariable partial-correlation analysis, the association between changes in the L/A ratio and TNF-α remained significant after controlling for baseline age, sex, and BMI (partial $r = 0.354$, $P = 0.031$; Table 6 and Fig. 2). This finding suggests that control of systemic inflammation may relate not only to macroscopic reductions in adipose-tissue volume but also to changes in local adipose paracrine function [9, 16, 19].

Chronic low-grade inflammation in severe obesity is commonly accompanied by monocyte infiltration into adipose tissue and differentiation into pro-inflammatory M1 macrophages [4, 19]. In this microenvironment, elevated leptin can exhibit pro-inflammatory properties. High circulating leptin may bind to OBRb receptors on macrophages and activate Janus kinase 2/signal transducer and activator of transcription 3 and nuclear factor kappa B pathways. These pathways promote transcription and production of TNF-α, interleukin-6, and interleukin-1 beta [20]. In the present study, aerobic exercise combined with energy restriction markedly reduced serum leptin and may have attenuated leptin-mediated inflammatory feedback [14, 17].

The compensatory increase in circulating adiponectin after the intervention may also have exerted an immunoregulatory effect [9]. Adiponectin can bind to adiponectin receptors 1 and 2 on adipose tissue and peripheral immune cells, thereby activating AMPK and peroxisome proliferator-activated receptor gamma pathways [21]. Previous studies suggest that these pathways can partly inhibit nuclear translocation of nuclear factor kappa B and suppress expression of pro-inflammatory mediators. They may also promote macrophage polarization from the M1 phenotype toward the reparative and anti-inflammatory M2 phenotype, thereby increasing secretion of anti-inflammatory mediators such as interleukin-10 [19, 21].

Contracting skeletal muscle also exhibits endocrine activity during exercise and releases exerkines, including muscle-derived interleukin-6 [22]. Unlike the sustained pro-inflammatory interleukin-6 secreted by macrophages in obesity, transient exercise-induced muscle-derived interleukin-6 may stimulate interleukin-1 receptor antagonist and interleukin-10 production. It may thereby inhibit TNF-α synthesis by macrophages [22]. Overall, the decrease in the L/A ratio suggests improvement in the local adipose paracrine environment. Together with exerkine regulation, this change may help alleviate chronic low-grade inflammation and reduce sustained inflammatory stimulation of the vascular wall.

3.4 Improvements in Vasomotor Homeostasis and Characteristics of Endothelial Adaptation

As central obesity and chronic low-grade inflammation improved, the participants showed signs of improved vascular endothelial function. After 4 weeks, serum nitric oxide (NO) increased and endothelin-1 (ET-1) decreased. The median NO/ET-1 ratio increased from 2.06 to 7.77 ($P < 0.001$). Soluble intercellular adhesion molecule-1, a marker of endothelial activation, also showed a downward trend. These cardiovascular biomarker changes are broadly consistent with recent meta-analyses of interventions in adolescents with obesity [13, 23].

From a hemodynamic perspective, aerobic exercise increases cardiac output and blood-flow velocity, thereby increasing laminar shear stress on the vascular wall [24, 25]. Endothelial sensing of this mechanical stimulus can activate intracellular phosphoinositide 3-kinase/protein kinase B and AMPK pathways. These pathways promote phosphorylation of endothelial nitric oxide synthase and increase endogenous NO release [24–26]. Higher NO

availability may relax vascular smooth muscle, suppress ET-1 transcription through negative feedback, and partly neutralize superoxide anions induced by dyslipidemia. These mechanisms provide a physiological basis for improvement in obesity-related vasomotor imbalance [9].

Improvement in the local anti-inflammatory microenvironment may also have contributed to endothelial protection. In severe obesity, excess TNF-α and interleukin-6 activate nuclear factor kappa B signaling in endothelial cells. This process induces adhesion molecules such as intercellular adhesion molecule-1 and promotes monocyte infiltration into the vascular intima [19, 27]. In the present study, improvement in the L/A ratio and a decrease in systemic TNF-α reduced the paracrine pro-inflammatory stimulus to endothelial cells. The accompanying reduction in soluble intercellular adhesion molecule-1 suggests that short-term lifestyle intervention may attenuate endothelial inflammatory activation and cell adhesion [9, 19].

Analysis of endothelial injury markers identified a noteworthy pattern. After adjustment for baseline age, sex, and BMI, the partial-correlation analysis and scatter plot showed a significant negative association between changes in hs-CRP and vWF (partial r = -0.342, P = 0.038; Table 6 and Fig. 3). Inflammation resolution is generally expected to accompany a decrease in injury markers. The observed inverse association may be interpreted in terms of differing physiological time courses of adaptation to exercise.

Physiologically, vWF is stored mainly in endothelial Weibel-Palade bodies. Its secretion is stimulated not only by chemical inflammatory mediators but also by changes in shear stress and direct endothelial remodeling [24, 25]. The vasculature of adolescents with obesity is chronically exposed to lipotoxic stress. During the early stage of the 4-week aerobic exercise program, circulating inflammatory markers decreased rapidly, as reflected by the reduction in hs-CRP. Meanwhile, sustained shear stress may have promoted cytoskeletal reorganization and matrix repair in injured endothelial cells [25, 26]. This physical process may have induced transient release of vWF from Weibel-Palade bodies within a limited time window.

The negative association between hs-CRP and vWF may therefore indicate that circulating inflammatory mediators were cleared faster than the vascular endothelium adapted mechanically to shear stress during the early intervention period [13, 24]. This proposed time lag suggests that biochemical improvement and tissue remodeling may not proceed synchronously during short-term exercise adaptation. Complete stabilization of endothelial structure may require longer observation. Nevertheless, the increased NO/ET-1 ratio and decreased soluble intercellular adhesion molecule-1 suggest that 4 weeks of exercise combined with dietary control improved vasomotor function in high-risk adolescents with obesity. These observations provide practical support for lifestyle interventions aimed at reducing cardiovascular risk during childhood [9, 13, 23].

3.5 Limitations and Future Directions

This study has several limitations. First, the single-group pre-post design could not fully distinguish the independent contributions of aerobic exercise and dietary control to endothelial recovery. Second, the 4-week intervention represented a short observation period, and long-term follow-up was unavailable to assess the durability of cardiovascular benefits. Third, the analysis of microscopic shear stress and endothelial adaptation relied mainly on serum biomarkers and did not include imaging-based reference measures such as ultrasound flow-mediated dilation.

Future studies should include large randomized controlled trials and long-term longitudinal follow-up. Circulating molecular biomarkers should be integrated with noninvasive vascular-function imaging to characterize exercise-related endothelial remodeling from multiple perspectives. The clinical cutoff for the L/A ratio should also be validated in broader populations of children and adolescents. Such evidence would strengthen the basis for individualized exercise and dietary prescriptions for metabolically high-risk groups.

Conclusion

This study showed that a 4-week intensive residential lifestyle intervention combining regular aerobic exercise with dietary control reduced BMI, body fat percentage, and measures of central obesity in adolescents with obesity. The intervention also improved basic glucose and lipid metabolism and vasomotor homeostasis, as reflected by the NO/ET-1 ratio.

Despite similar reductions in body composition, metabolic responses varied according to the baseline L/A ratio. Children in the high-risk group (L/A ratio > 4.64) showed greater improvements in insulin resistance and triglyceride reduction. After adjustment for baseline confounders, resolution of systemic low-grade inflammation was closely associated with improvement in the adipose paracrine microenvironment. The clearance of acute circulating inflammatory markers also appeared to precede mechanical remodeling of vascular endothelial structure, suggesting different time courses for biochemical improvement and tissue repair during short-term exercise adaptation.

Overall, the L/A ratio may serve as a biomarker for cardiometabolic risk stratification in adolescents with obesity. Early combined exercise and dietary intervention in high-risk groups may promote deeper metabolic remodeling and endothelial recovery in addition to improving external body morphology. This approach may have practical value for the early prevention and control of chronic disease in children and adolescents with obesity.

Declarations

Ethics approval and consent to participate

The original study protocol was approved by the Scientific Research Ethics Committee of Shanghai University of Sport (Approval No. 102772024RT158). The present study was an exploratory secondary analysis of data from the same cohort and samples collected under the approved protocol. The study population, exercise and dietary intervention, sample collection, and biomarker measurements analyzed in this manuscript were covered by the original ethics approval. Written informed consent was obtained from all participants and their legal guardians before study participation. This secondary analysis involved no additional intervention or sample collection and introduced no additional risk to participants.

Consent for publication

Not applicable. This manuscript contains no identifiable individual participant information or images.

Competing interests

The authors declare that they have no competing interests.

Funding

This work was supported by the General Project of Shanghai Education Science Research (Grant No. C2026153).

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Funding

This work was supported by the General Project of Shanghai Education Science Research (Grant No. C2026153).

Author Contribution

Y.C. contributed to data curation, formal analysis, visualization, and preparation of the original draft. Y.S. contributed to conceptualization, methodology, supervision, project administration, funding acquisition, and review and editing of the manuscript. Both authors read and approved the final manuscript.

Acknowledgements

The authors thank all participants and their legal guardians for their participation and cooperation.

Data Availability

The data in this study were obtained from the experiment.

References

1. Pan XF, Wang L, Pan A. Epidemiology and determinants of obesity in China. Lancet Diabetes Endocrinol. 2021;9(6):373–92. 10.1016/S2213-8587(. 21)00045-0 PubMed PMID: 34022156.
2. Dong Y, Chen L, Liu J, Ma T, Zhang Y, Chen M, et al. Epidemiology and prediction of overweight and obesity among children and adolescents aged 7–18 years in China from 1985 to 2019. Chin J Prev Med. 2023;57(4):461–9. 10.3760/cma.j.cn112150-20220906-00881.
3. Umer A, Kelley GA, Cottrell LE, Giacobbi P, Innes KE, Lilly CL. Childhood obesity and adult cardiovascular disease risk factors: A systematic review with meta-analysis. BMC Public Health. 2017;17(1):683. 10.1186/s12889-017-4691-z . PubMed PMID: 28851330; PubMed Central PMCID: PMC5575877.
4. Singer K, Lumeng CN. The initiation of metabolic inflammation in childhood obesity. J Clin Invest. 2017;127(1):65–73. doi:10.1172/JCI88882 PubMed PMID: 28045405; PubMed Central PMCID: PMC5199687.
5. Pozo Giráldez A, Bravo Gómez A, Calmarza P, Sienes Bailo P, Dayaldasani Khialani A, Montolio Breva S, et al. Oxidative stress and its role in vascular damage and atherosclerosis. Int J Mol Sci. 2026;27(2):1075. 10.3390/ijms27021075.
6. Kopych V, Da Costa ADS, Park K. Endothelial dysfunction in atherosclerosis: Experimental models and therapeutics. Biomater Res. 2025;29:0252. 10.34133/bmr.0252.
7. Shang YX, Chen PJ, Chen WH. Effects of aerobic exercise on serum soluble intercellular adhesion molecule-1 in obese adolescents. J Shanghai Univ Sport. 2010;34(6):46–9. [In Chinese].
8. Shang YX, Hou XH, Pan SS, et al. Effects of aerobic exercise on cardiovascular risk factors in different obesity subtypes of children. Chin J Sports Med. 2022;41(4):266–73. 10.16038/j.1000-6710.2022.04.001. . [In Chinese].
9. Valenzuela PL, Carrera-Bastos P, Castillo-García A, Lieberman DE, Santos-Lozano A, Lucia A. Obesity and the risk of cardiometabolic diseases. Nat Rev Cardiol. 2023;20(7):475–94. 10.1038/s41569-023-00847-5 . PubMed PMID: 36927772.
10. Vissers D, Hens W, Taeymans J, Baeyens JP, Poortmans J, Van Gaal L. The effect of exercise on visceral adipose tissue in overweight adults: A systematic review and meta-analysis. PLoS ONE. 2013;8(2):e56415.

10.1371/journal.pone.0056415 . PubMed PMID: 23409182; PubMed Central PMCID: PMC3568069.

11. Verheggen RJHM, Maessen MFH, Green DJ, Hermus ARMM, Hopman MTE, Thijssen DHT. A systematic review and meta-analysis on the effects of exercise training versus hypocaloric diet: Distinct effects on body weight and visceral adipose tissue. Obes Rev: Off J Int Assoc Study Obes. 2016;17(8):664–90. 10.1111/obr.12406 . PubMed PMID: 27213481.
12. Després JP, Lemieux I. Abdominal obesity and metabolic syndrome. Nature. 2006;444(7121):881–7. 10.1038/nature05488 . PubMed PMID: 17167477.
13. García-Hermoso A, López-Gil JF, Izquierdo M, Ramírez-Vélez R, Ezzatvar Y. Exercise and insulin resistance markers in children and adolescents with excess weight: A systematic review and network meta-analysis. JAMA pediatr. 2023;177(12):1276–84. 10.1001/jamapediatrics.2023.4038 . PubMed PMID: 37812414; PubMed Central PMCID: PMC10562991.
14. Xin X, Guo Y, Liu L, Liu Q, Xie J. Effects of exercise alone or combined with dietary restriction on leptin and adiponectin in overweight or obese individuals: A network meta-analysis. BMC Sports Sci Med Rehabil. 2025;17(1):295. 10.1186/s13102-025-01316-x . PubMed PMID: 41088455; PubMed Central PMCID: PMC12523059.
15. Saltiel AR. Insulin signaling in health and disease. J Clin Invest. 2021;131(1):e142241. 10. 1172/JCI142241 PubMed PMID: 33393497; PubMed Central PMCID: PMC7773347.
16. Agostinis-Sobrinho C, Vicente SE, de CF, Norkiene S, Rauckienė-Michaelsson A, Kievisienė J, Dubey VP, et al. Is the adiponectin ratio a better diagnostic biomarIs the leker for insulin resistance than leptin or adiponectin alone in adolescents? Children. 2022;9(8):1193. 10.3390/children9081193 . PubMed PMID: 36010082; PubMed Central PMCID: PMC9406389.
17. Jeong D, Valentine RJ, Park K, Jeong H, Hong J, Kang S. Effect of exercise on hormonal responses in adolescents with obesity and leptin resistance: A randomized trial. Sci Rep. 2026;16(1):4099. 10.1038/s41598-026-36045-9 . PubMed PMID: 41535443; PubMed Central PMCID: PMC12855297.
18. Sirico F, Bianco A, D'Alicandro G, Castaldo C, Montagnani S, Spera R, et al. Effects of physical exercise on adiponectin, leptin, and inflammatory markers in childhood obesity: Systematic review and meta-analysis. Child Obes. 2018;14(4):207–17. 10.1089/chi.2017.0269 . PubMed PMID: 29762052; PubMed Central PMCID: PMC5994661.
19. Longo M, Zatterale F, Naderi J, Parrillo L, Formisano P, Raciti GA, et al. Adipose tissue dysfunction as determinant of obesity-associated metabolic complications. Int J Mol Sci. 2019;20(9):2358. 10.3390/ijms20092358 . PubMed PMID: 31085992; PubMed Central PMCID: PMC6539070.
20. Leptin resistance. A possible interface of inflammation and metabolism in obesity-related cardiovascular disease. J Am Coll Cardiol. 2008;52(15):1201–10. 10.1016/j.jacc.2008.05.060.
21. Sun H, Zhang Y, Shi L. Advances in exercise-induced vascular adaptation: mechanisms, models, and methods. Front Bioeng Biotechnol. 2024;12:1370234. 10.3389/fbioe. 2024.1370234 PubMed PMID: 38456010; PubMed Central PMCID: PMC10917942.
22. Chow LS, Gerszten RE, Taylor JM, Pedersen BK, van Praag H, Trappe S, et al. Exerkines in health, resilience and disease. Nat Rev Endocrinol. 2022;18(5):273–89. 10.1038/s41574-022-00641-2 . PubMed PMID: 35304603; PubMed Central PMCID: PMC9554896.
23. Bruyndonckx L, Hoymans VY, Lemmens K, Ramet J, Vrints CJ. Childhood obesity-related endothelial dysfunction: an update on pathophysiological mechanisms and diagnostic advancements. Pediatr Res. 2016;79(6):831–7. 10.1038/pr.2016.22 . PubMed PMID: 26866906.
24. Green DJ, Hopman MTE, Padilla J, Laughlin MH, Thijssen DHJ. Vascular adaptation to exercise in humans: Role of hemodynamic stimuli. Physiol Rev. 2017;97(2):495–528. 10.1152/physrev.00014. .2016 PubMed PMID: 28151424;

PubMed Central PMCID: PMC5539408.

25. Zhang X, Liu J, Ni Y, Yi C, Fang Y, Ning Q et al. Global prevalence of overweight and obesity in children and adolescents [Internet]. 10.1001/jamapediatrics.2024.1576
26. Thijssen DHJ, Bruno RM, van Mil ACCM, Holder SM, Faita F, Greyling A, et al. Expert consensus and evidence-based recommendations for the assessment of flow-mediated dilation in humans. Eur Heart J. 2019;40(30):2534–47. 10.1093/eurheartj/ehz350 . PubMed PMID: 31211361.
27. Fuster JJ, Ouchi N, Gokce N, Walsh K. Obesity-induced changes in adipose tissue microenvironment and their impact on cardiovascular disease. Circ Res. 2016;118(11):1786–807. 10.1161/CIRCRESAHA.115.306885 . PubMed PMID: 27230642; PubMed Central PMCID: PMC4887147.

Figures

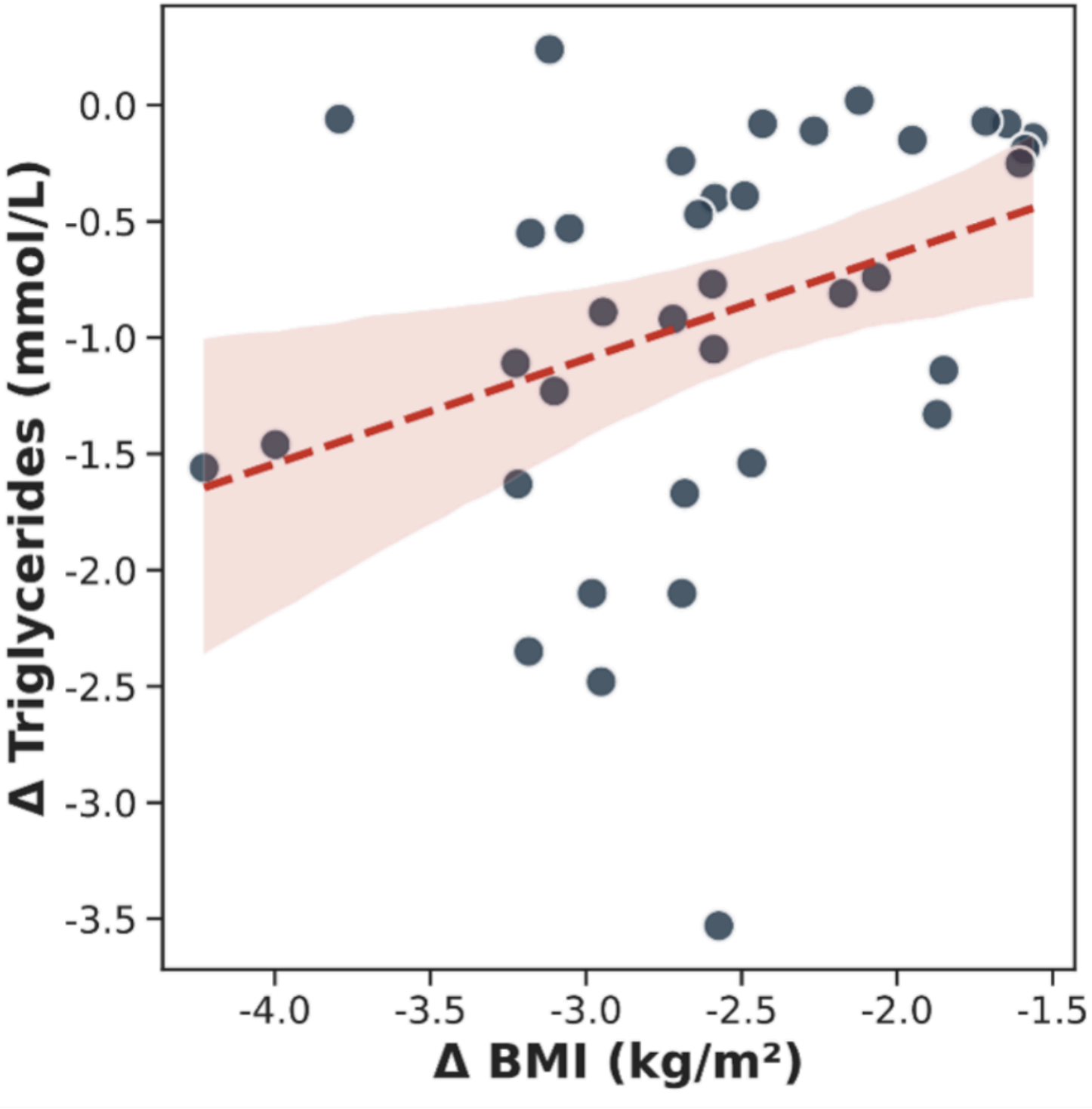


Figure 1

Scatterplot showing the positive correlation between ΔBMI and ΔTG.

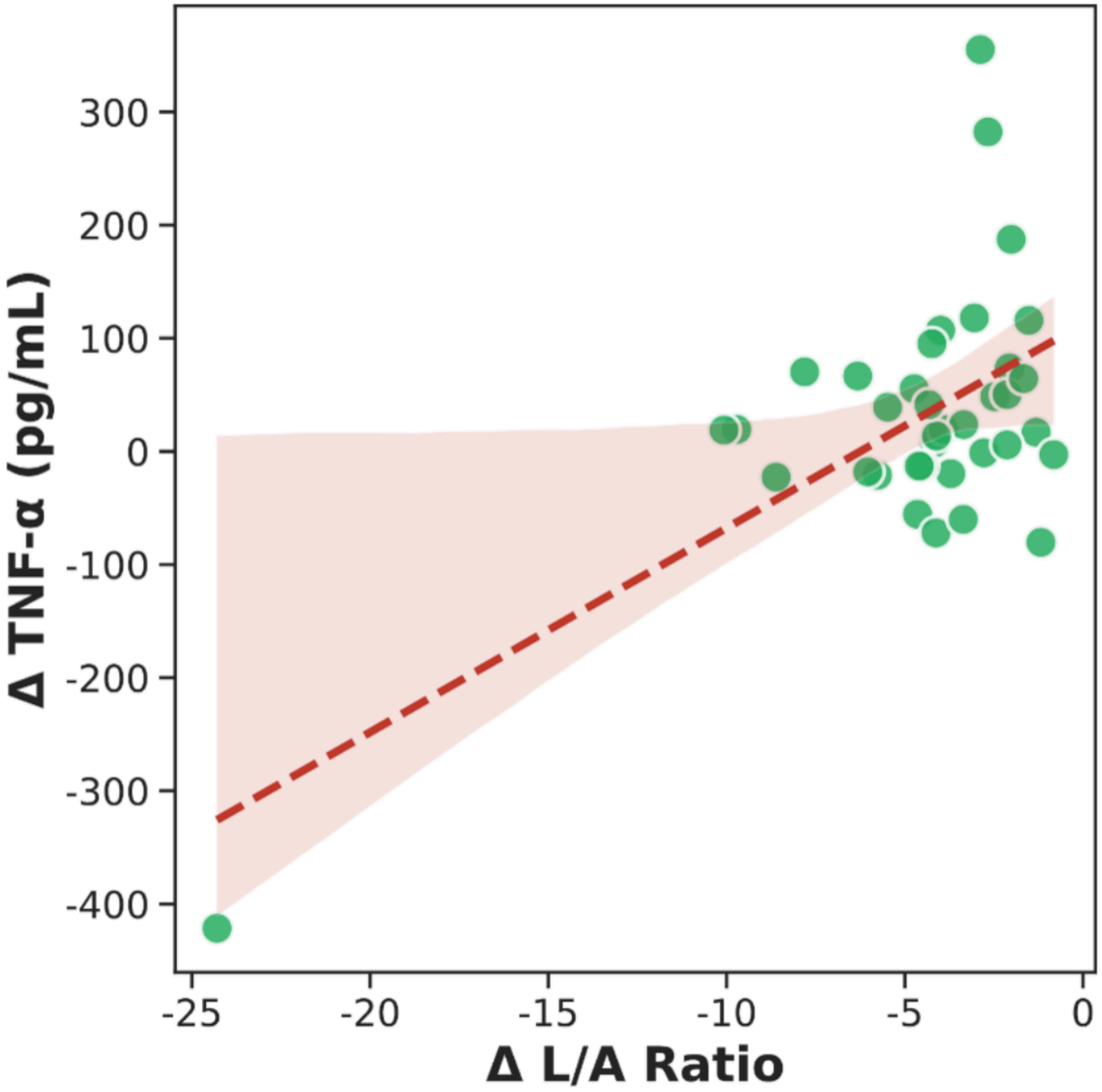


Figure 2

Scatterplot showing the positive correlation between ΔL/A ratio and ΔTNF-α.

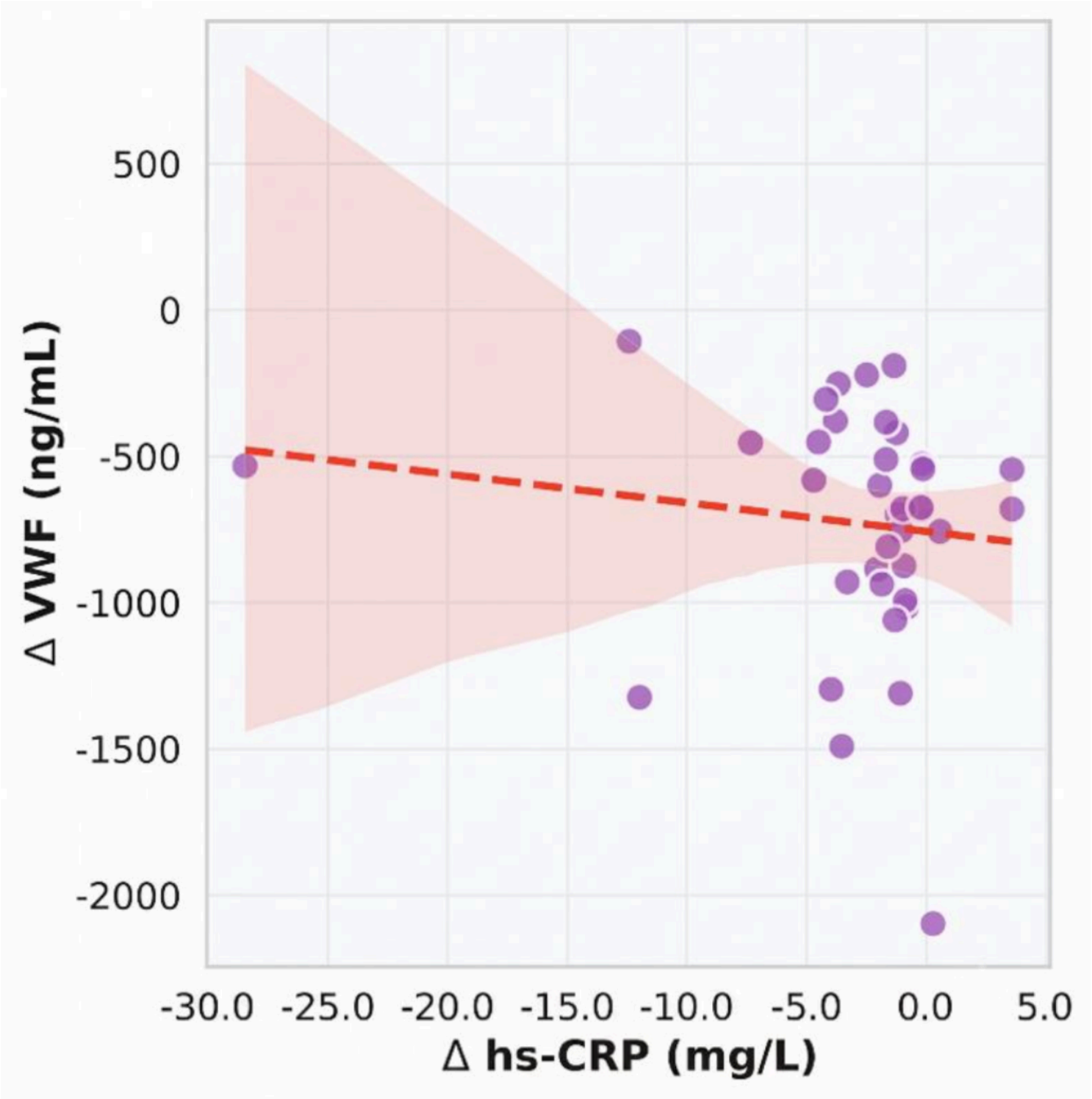


Figure 3

Scatterplot showing the negative correlation between Δhs-CRP and ΔvWF.