Published in final edited form as:

J Pediatr. 2018 November ; 202: 143–149. doi:10.1016/j.jpeds.2018.06.047.

Early Life Adversity with Height Stunting Is Associated with Cardiometabolic Risk in Adolescents Independent of Body Mass Index

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Abstract

Objective—To evaluate cardiovascular and metabolic function in youths adopted internationally from orphanages/institutions (postinstitutionalized) who were height-stunted at adoption.

Study design—A total of 30 postinstitutionalized youths (age, 9–18 years; body mass index [BMI] percentile, 7.2–90.4) who were height-stunted at adoption were compared with age- and BMI percentile-matched youths ($n = 90$). Measurements included total body fat and visceral adipose tissue (dual radiograph absorptiometry), arterial stiffness (augmentation index and pulse wave velocity), cardiac autonomic function (heart rate variability), blood pressure, and fasting lipid, glucose, and insulin levels. Linear regression analyses were computed controlling for parent education, age, trunk tissue fat, height-for-age, sex, and race.

Results—Compared with controls of the same age, sex, and BMI, the postinstitutionalized children had higher systolic blood pressure ($P = .018$), augmentation index ($P = .033$), total cholesterol ($P = .047$), low-density lipoprotein cholesterol ($P = .03$), triglycerides ($P = .048$), insulin ($P = .005$), and HOMA-IR ($P = .01$) values. The postinstitutionalized children had a lower low-frequency to high-frequency ratio ($P = .008$), indicating lower sympathetic tone, as well as a lower total lean mass ($P = .016$), a lower gynoid lean mass ($P = .039$), and a higher proportion of trunk tissue fat ($P = .017$). The postinstitutionalized and control children did not differ in any other body composition measures.

Conclusions—Early life stress, as represented by height-stunted growth in institutional care, may be associated with early pathways to cardiovascular and metabolic risk in youths even after moving into well-resourced homes early in life and in the absence of increased adiposity. These

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We thank the families for their participation in the International Adoption Project, and thank Bonny Donzella, Bao Moua, Cameron Naughton, and Heather Taylor for their assistance with the study. We also thank the Center for Neurobehavioral Development and Clinical Translational Science Institute at the University of Minnesota.

findings suggest that postinstitutionalized youths with a history of height stunting may need to be closely monitored for emergent cardiometabolic risk factors.

Over the last 25 years, more than 300 000 children have been adopted internationally into the US, with the majority coming from institutional (ie, orphanage) care.^{1,2} Many arrive to their new families growth-delayed, with a significant percentage meeting the criteria for mild (-1.5 z-score height-for-age) or moderate height stunting (-2 z-score height-for-age). Families who adopt internationally tend to be of higher income and education,³ and within a short period following adoption, most children fall within age norms for height and weight.⁴ The early life histories of these children, combined with the evidence of poor growth before adoption and with rapid catch-up thereafter, theoretically should increase their risk for early-onset puberty and obesity,^{5,6} ultimately leading to increased risk of developing cardiometabolic problems.⁷

Our research group found that youths adopted internationally from orphanages (postinstitutionalized) at age 7-14 years tended to be lean, and females did not exhibit early pubertal onset.⁸ This was true also of the 25% of the sample who were severely height-stunted at adoption.⁸ However, because body mass index (BMI) is only one measure of metabolic risk, it is possible that postinstitutionalized youths may have higher levels of total body fat and/or a greater degree of fat mass distributed in the visceral adipose tissue (VAT) depots,⁹ which may increase cardiovascular risk.^{10,11} It is also possible that postinstitutionalized youths have additional metabolic and cardiovascular risks that are not captured by a measure of BMI. Early life stress has been found to contribute to metabolic dysregulation in cholesterol, insulin, glucose, triglycerides, and adipose tissue.^{12,13} Cardiac autonomic function, characterized by activation of the sympathetic nervous system, and measures of vascular health, such as arterial stiffness, may contribute independently to the development of cardiovascular disease later in life.¹⁴⁻²¹ This study follows our previous work and includes predictors of metabolic and cardiovascular functioning.

Methods

One-hundred and twenty youths (60 females), aged 8-18 years, were included in this study. Data were obtained from 2 cohorts: a cohort of postinstitutionalized youths and a control cohort of nonadopted youths living in the Minneapolis-Saint Paul metropolitan area. Both study protocols were approved by the University of Minnesota's Institutional Review Board, and consent/assent was obtained from parents/participants.

The postinstitutionalized cohort ($n = 30$; 19 females) consisted of youths recruited from a registry of internationally adopting families. Participants were included if their adoption medical records indicated a height-for-age z-score ≥ -1.5 , defined as mild height stunting.²² Mild height stunting served as an inclusion criterion both to increase the postinstitutionalized recruitment pool and to include a gradation of growth faltering that often continues to decline until around age 2 years.^{23,24} Exclusion criteria included current steroid medication use, ongoing or chronic infections, acute congenital and endocrine disorders, fetal alcohol syndrome, and pregnancy. Exclusion criteria also included adoption after age 3 years, to investigate early insults to growth. All postinstitutionalized cohort

testing was conducted in the Delaware Clinical Research Unit at the University of Minnesota, Twin Cities.

In the control cohort (n = 90; 57 females), data were collected from youths who participated in a cross-sectional study examining cardiovascular risk factors in youths ranging in weight from normal to severe obesity. Participants were recruited from local medical clinics and advertisements. Participants were excluded if they were taking medications known to influence cardiovascular function or had known/diagnosed cardiovascular disease. This cohort has been described in more detail elsewhere.²⁵ Controls were identified from this sample of 300 youths by matching 3:1 with cases by age and weight status. Testing in both cohorts was performed in the morning, with the participants fasted and also fully abstinent from tobacco, alcohol, and caffeine, for a minimum of 8 hours before their study visit.

Measurements for height and body mass were obtained using a wall-mounted stadiometer and electronic scale, respectively. BMI was calculated as body mass in kilograms divided by height in meters squared. BMI percentile was calculated using Centers for Disease Control normality scales and stratified into 3 categories: normal weight (>5th to <85th percentile), overweight (85th to <95th percentile), and obese (≥95th percentile).²⁶ Body composition was measured by dual X-ray absorptiometry (iDXA; GE Healthcare, Madison, Wisconsin) and analyzed using enCore version 16.2 (GE Healthcare). VAT was estimated using CoreScan (GE Healthcare) as described previously.²⁷⁻²⁹ Seated blood pressure in the right arm was measured after the participant rested for 10 minutes with legs uncrossed using an automated sphygmomanometer (BP-8800; Colin Medical Instruments, San Antonio, Texas). Blood pressure percentiles were determined from age, sex, and height using the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents.³⁰ A blood lipid panel, fasting glucose, and fasting insulin were measured (Fairview Diagnostic Laboratories, Fairview University Medical Center, Minneapolis, Minnesota). Plasma glucose levels were measured by the bichromatic endpoint (Fairview Diagnostic Laboratories). Insulin levels were measured with a chemiluminescent immunoassay (ADVIA Centaur System; Siemens Healthcare Diagnostics, Tarrytown, New York). The homeostasis model assessment–estimated insulin resistance (HOMA-IR) score was calculated from a standard equation from fasting plasma glucose and insulin levels.³¹

Right radial, and carotid artery waveforms, as well as carotidradial pulse wave velocity (PWV), were recorded by applanation tonometry using SphygmoCor MM3 version 8.0 software (AtCor Medical, Sydney, Australia). Radial and carotid artery augmentation index (AIx), both corrected to a heart rate of 75 bpm, were derived from a validated integral transfer function applied by SphygmoCor MM3. PWV was measured by the sequential acquisition of pressure waveforms from the carotid and radial artery using the same tonometer. Carotidradial PWV was calculated from the transit time between the 2 arteries relative to the R-wave within the electrocardiography (ECG) complex, using the foot-to-foot method and the intersecting tangent algorithm.³²⁻³⁴

Autonomic nervous system activity was assessed by heart rate variability (HRV) using the same SphygmoCor MM3 system. Using a 3-lead ECG in a modified lead II configuration, Heart rate was recorded continuously for 5 minutes. All ECG recordings were reviewed and

analyzed for time and frequency domains, with segments demonstrating arrhythmias excluded from the analysis. Time domain variables, such as the mean R-R interval length, standard deviation of R-R intervals, number of adjacent intervals >50 ms, and percentage of adjacent intervals >50 ms, were obtained from automated algorithms provided by the SphygmoCor software.^{25,35} Spectral analysis calculated frequency-domains, including low frequency (LF), high frequency (HF), LF:HF ratio, and total power.²⁵ Frequencies of 0.04-0.15 Hz and 0.15-0.40 Hz were defined as LF and HF, respectively.²⁵

Self-report questionnaires determined parent education and race. Parent education was recorded as either 1, obtained a college degree (associate's degree or above), or 0, no college degree. Race was defined as 0, white, or 1, nonwhite.

Statistical Analyses

Descriptive statistics were tabulated separately for postinstitutionalized and control subjects. The *P* values presented in Table I were based on *t* tests for continuous covariates and χ^2 tests for categorical covariates. Outliers were winsorized, and skewed distributions were log-transformed for analyses. Multiple imputation by chained equations was used with 50 repetitions to impute missing data.³⁶ Results between the complete-case analysis and nonimputed dataset were similar; thus, imputed results are presented. Regression analyses were conducted on all outcomes to assess differences between groups and adjusted for sex, race, age, BMI percentile, height-for-age, and parent education. Vascular, hemodynamic, and biochemical variables were also adjusted for trunk tissue fat percentage. Covariates were selected a priori for their role as potential confounders or precision variables. All statistical analyses were performed with R version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria) and the “mice” library version 2.46.0.

Results

The groups did not differ in age or sex distribution, although the proportion of white patients was higher in the control group compared with the postinstitutionalized group (Table I). The height-for-age *z*-score showed that the postinstitutionalized youths were smaller for age than the comparison group, though the averages for both groups were in the normal range. The postinstitutionalized youths were more likely to have lower overall lean mass and lower gynoid lean mass (Table II). They were also more likely to have a higher percentage of trunk tissue fat, but did not differ from controls in the amount of VAT. The postinstitutionalized youths and control youths did not differ in any other measures of body fat mass.

The postinstitutionalized youths exhibited higher systolic blood pressure than control youths, though there was no difference in either systolic blood pressure percentile or in either measure of diastolic blood pressure (Table III).¹⁰ The postinstitutionalized youths had a lower LF:HF compared with controls. They also had higher carotid Aix values. Carotid Aix and systolic blood pressure percentile were both independently predicted by group membership (Table IV). Postinstitutionalized status did not predict carotid-radial PWV.

Blood test results are displayed in Table IV. The postinstitutionalized group had higher total cholesterol, low-density lipoprotein cholesterol, triglycerides, and insulin levels. There were no between-group differences in high-density lipoprotein and glucose levels. HOMA-IR was also higher in the postinstitutionalized youths.

Discussion

These findings demonstrate a potential association between early life adversity and later childhood development of cardiometabolic risk factors and arterial stiffness. These risks appear to be independent of BMI and trunk tissue fat in these postinstitutionalized youths who were mildly to severely height-stunted at adoption. Postinstitutionalized youths, exposed to psychosocial adversity and growth adversity before age 3 years, demonstrated higher systolic blood pressure, evidence of arterial stiffening, and evidence of higher total cholesterol, low-density lipoprotein cholesterol, triglycerides, and insulin levels and HOMA-IR scores. Importantly, these associations were found to be independent of body composition as the majority of youths in the postinstitutionalized group were well within healthy norms for body composition and, because the comparison group was selected to be consistent with the postinstitutionalized group, this was true of the comparison group as well. In addition, the postinstitutionalized youths demonstrated a less sympathetically driven cardiovascular system. These results suggest that children with a history of early life stress and malnutrition might be at higher risk for cardiometabolic health problems even compared with youths with a similar BMI.

Although previous work by our group had shown normal BMI in postinstitutionalized youths,⁸ we questioned whether more rigorous tests might reveal greater accumulation of fat in the viscera. Nonetheless, although evidence suggests that the physiological mechanisms of catch-up growth promote the accumulation of VAT after nutritional deprivation,⁵ this was not observed in these postinstitutionalized youths. Instead, the postinstitutionalized youths were also more likely to have a higher percentage of trunk tissue fat, but not of VAT specifically. Indeed, results on early growth stunting and later visceral adiposity have been mixed.³⁷ An obesogenic environment may be the critical component in the association of early life catch-up growth with later obesity and/or increased VAT.³⁸

Arterial stiffness is indicated by both AIx and PWV. Augmentation index measures the relative magnitude of the reflected (ie, retrograde) pulse wave early in the cardiac cycle, with greater values indicating increased arterial stiffening.¹⁴ Pulse wave transit time increases within stiffer arteries and is manifested by higher PWV values.¹⁴ The postinstitutionalized youths had higher carotid Aix values after controlling for parent education, race, age, sex, height for age, trunk tissue fat, and BMI percentile. In contrast, there were no differences in PWV between the postinstitutionalized and control groups. Arterial stiffness is an independent risk factor for cardiovascular disease in adults¹⁶ and has been shown to be associated with cardiovascular risk factors and excess adiposity in children.³⁹⁻⁴¹

The HRV results were mixed. The postinstitutionalized youths exhibited a lower LF:HF than control youths, yet differed in no other measures of HRV. The LF:HF is considered a measure of the autonomic nervous system's overall sympathovagal balance, with lower

values indicating a less sympathetically driven cardiovascular system.^{42,43} This less sympathetically driven system is consistent with a Romanian study of postinstitutionalized youths who showed lower sympathetic nervous system reactivity to a psychosocial challenge compared with children reared in their families.⁴⁴ In both this study and the study of postinstitutionalized youths in Romania, youths with a history of early life adversity were prone to experiencing a “down-regulated” sympathetic nervous system response.^{45,46} The postinstitutionalized mean LF:HF of 0.6 is also lower than the expected range of 1.1-11.6 reported in other studies with adults.⁴⁷ Because sympathetic tone is associated with increasing age, postinstitutionalized youths might experience increased LF:HF as they age.⁴⁷ Alternatively, LF:HF may be an early indicator of less optimal HRV for postinstitutionalized youths later in life, despite other measures of HRV that do not exhibit increased risk.

Postinstitutionalized children exhibited higher systolic, but not diastolic, blood pressure. Previous studies of the association between adverse childhood experiences and blood pressure have shown mixed results. There have been few studies of adolescents with a history of adverse childhood experiences that report blood pressure metrics, and the results of these studies have shown either no relationship between adverse early experiences and blood pressure or a relationship between early adversity and diastolic, but not systolic, blood pressure.^{48,49}

Increased plasma cholesterol has been identified as playing a key role in arterial impairment and a higher augmentation index in a pediatric population.⁵⁰ The results from this postinstitutionalized cohort suggest that the combination of higher plasma cholesterol levels and increased carotid augmentation index could put children with early adversity at risk for cardiometabolic dysfunction without the presence of obesity.

Postinstitutionalized youths in this study exhibited higher insulin levels than controls. The higher HOMA-IR scores seen in the postinstitutionalized group, although consistent with the group’s higher levels of insulin, exist without a significantly higher glucose level. Although the mean HOMA-IR scores are not above the HOMA-IR cutoff scores for insulin resistance for either prepubertal or pubertal youths, this increase without the presence of obesity could signal cardiometabolic risk for youths with a history of early life adversity and height stunting.⁵¹

This study has a number of important limitations. First, the study consists of a small, cross-sectional sample, and so we are unable to make causal claims. Second, we do not have information on gestational age or birth weight for either cohort. This information is not available at all for most postinstitutionalized youths, and thus we are unable to comment on how gestational age and birth weight play a role in metabolic or cardiovascular differences between the groups. Catch-up growth from preterm or low birth weight might influence the results and represent a risk to the postinstitutionalized youths distinct from their postnatal adversity. Low birth weight is overrepresented in postinstitutionalized youths compared with other groups, and thus the effects seen in this study might come not from early life stress and malnutrition, but rather from low birth weight.⁵² In a similar vein, we are unable to make claims about the adversity that the control cohort may or may not have experienced early in life, in either a psychosocial or a physical domain. We do not have data on the height-for-age

of the control cohort at an age comparable with the age of adoption in the postinstitutionalized cohort, and thus we are unable to comment on the linear growth of the control cohort early in life.

A third limitation is the absence of the measurement of health behaviors in this study. We are unable to make claims about the participants' current health behaviors. Diet may play a large role in mediating the relationship between early life adversity, growth restriction, and later risks to cardiovascular and metabolic health. It is not yet clear how these youths' diets may impact their current or future health. As continued research suggests that psychosocial stress may induce emotional overeating,⁵³⁻⁵⁶ emotional eating in individuals with a history of adversity could lay the groundwork for later obesity and even higher risks of cardiometabolic disease.^{57,58} Thus, future studies would benefit from rigorously measuring and assessing diet as a covariate to account for differences that may influence the metabolic outcomes.

Finally, many outcomes were studied in this pilot study, and thus, with multiple testing, there could be increased risk for chance findings. Results should be interpreted cautiously. Future studies of cardiometabolic risk in postinstitutionalized youths would benefit from additional statistical power.

This study provides preliminary evidence that youths exposed to early life stress and growth stunting may be at greater risk of developing heart disease and metabolic disorders independent of BMI. Postinstitutionalized youths with a history of growth stunting may require close monitoring for emergent cardiometabolic risk. ■

Acknowledgments

Funded by the National Heart, Lung, and Blood Institute (R01 HL110957, to A.K.), the National Center for Advancing Translational Sciences (UL1TR000114), the National Institute of Diabetes and Digestive and Kidney Diseases (NORC Grant P30 DK050456), and the Canadian Institute for Advanced Research Child and Brain Development program (to M.G.). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. This material is based on work supported by the National Science Foundation Graduate Research Fellowship (Grant 00039202, to B.R.). Any opinion, findings, and conclusions or recommendations expressed in this material are those of the authors(s) and do not necessarily reflect the views of the National Science Foundation. A.K. serves as a consultant for Novo Nordisk, Orexigen, and Vivus Pharmaceuticals and receives research support from Astra Zeneca Pharmaceuticals in the form of drug/placebo. D.D. serves as a paid consultant for Hologic, Inc. The other authors declare no conflicts of interest.

Glossary

AIx	Augmentation index
BMI	Body mass index
ECG	Electrocardiography
HF	High frequency
HOMA-IR	Homeostasis model assessment–estimated insulin resistance
LF	Low frequency

PWV	Pulse wave velocity
VAT	Visceral adipose tissue

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Table I.

Participant demographic, anthropometric, and covariate characteristics by group status

Measures	Postinstitutionalized (n = 30)	Control (n = 90)	<i>P</i> value
Demographic data			
Age, y, mean (SD)	13.5 (3.26)	13.0 (2.94)	.476
Age at adoption, mo, mean (SD)	18.6 (9.98)	NA	—
Female sex, n (%)	19 (63.3)	41 (45.6)	.092
White race, n (%)	13 (43.3)	82 (91.1)	< .001
Anthropometric data			
Height-for-age z-score for at time of adoption, mean (SD)	−2.2 (.48)	—	—
Height-for-age z-score, mean (SD)	−0.8 (0.93)	0.2 (0.93)	< .001
BMI, kg/m ² , mean (SD)	19.8 (4.5)	19.8 (4.8)	.989
BMI percentile, mean (SD)	51.5 (31.5)	53.9 (26.8)	.681
Weight category, n (%)			
Normal	25 (83.3)	75 (83.3)	.953
Overweight	4 (13.3)	12 (13.3)	
Obese	1 (3.3)	3 (3.3)	
Waist circumference, cm, mean (SD)	67.9 (12.2)	66.2 (12.5)	.505
Hip circumference, cm, mean (SD)	79.3 (15.3)	82.1 (13.8)	.355

NA, not applicable.

BMI percentile reported as age- and sex-adjusted percentile (SD) based on Centers for Disease Control growth curves. Significant *P* values are in bold type.

Table II.

Anthropometric dual X-ray absorptiometry characteristics by group status

Measures	Postinstitutionalized (n = 30)	Control (n = 90)	Adjusted difference (95% CI)	P value
Lean mass, g	30 657.6 (11 636.7)	34 074.0 (12180.3)	-3039.6 (-5506.90 to -572.38)	.016
Fat mass, g	13 330.5 (7624.9)	13 163.7 (8759.3)	482.914 (-1593.46 to 2559.29)	.646
Total tissue fat, %	29.1 (8.2)	26.8 (7.4)	2.5 (-0.42 to 5.39)	.093
Trunk lean mass, g	14 399.1 (5623.9)	15 637.4 (5831.8)	-1200.9 (-2787.77 to 385.97)	.136
Trunk fat mass, g	5918.4 (4561.5)	5307.4 (4782.0)	740.5 (-594.96 to 2075.90)	.274
Trunk tissue fat, %	26.6 (10.6)	23.0 (9.1)	4.11 (0.74 to 7.49)	.017
Android lean mass, g	2050.8 (833.1)	2258.9 (834.6)	-183.1 (-366.67 to 0.51)	.051
Android fat mass, g	818.9 (847.4)	734.3 (872.7)	137.3 (-118.24 to 392.85)	.289
Gynoid lean mass, g	4586.8 (2092.1)	5075.6 (2189.8)	-487.2 (-949.97 to -24.42)	.039
Gynoid fat mass, g	2136.1 (1289.9)	2288.8 (1574.3)	-66.5 (-465.73 to 332.69)	.742
VAT mass, g	164.6 (208.2)	117.1 (151.4)	38.3 (-52.8 to 129.45)	.406

Values presented are mean (SD) and mean difference (95% CI), adjusted for age, sex, BMI percentile, current height-for-age, parent education (college vs others), and race (white vs others). Significant *P* values are in bold type.

Table III.

Autonomic nervous system activity and arterial stiffness by group status

Measure	Postinstitutionalized (n = 30), mean (SD)	Control (n = 90), mean (SD)	Adjusted difference (95% CI)	P value
Autonomic nervous system activity				
Heart rate, bpm	65.2 (7.71)	67.5 (10.12)	-3.4 (-8.76 to 2.01)	.216
SBP, mmHg	116.9 (10.5)	106.6 (10.46)	5.7 (1.02-10.4)	.018
SBP percentile	68.6 (25.06)	47.9 (27.45)	13.6 (-1.95 to 29.25)	.086
DBP, mmHg	60.7 (10.7)	58.7 (8.65)	1.4 (-5.60 to 8.36)	.693
DBP percentile	35.0 (24.0)	41.0 (29.32)	3.3 (-17.41 to 24.08)	.749
NN50	160.2 (60.77)	141.3 (65.82)	20.5 (-17.48 to 58.4)	.287
PNN50	50.0 (19.76)	45.6 (22.83)	6.3 (-6.66 to 19.30)	.336
Mean R-R interval, ms	933.1 (115.0)	912.9 (142.16)	42.1 (-30.88 to 115.15)	.255
SD R-R interval, ms	86.1 (40.8)	100.7 (58.97)	1.0 (0.72-1.44)	.921
LF:HF	.6 (.41)	1.1 (1.4)	-0.68 (-1.18 to -0.18)	.008
Arterial stiffness				
Carotid AIx	7.2 (10.97)	-6.4 (16.92)	10.0 (0.81-19.21)	.033
Radial AIx	4.6 (11.28)	1.2 (15.29)	0.4 (-9.31 to 10.12)	.934
Carotid-radial PWV	7.1 (1.35)	6.5 (1.27)	0.4 (-0.35 to 1.11)	.303

DBP, diastolic blood pressure; NN50, number of adjacent intervals over 50 ms; PNN50, percentage of adjacent intervals over 50 ms; SBP, systolic blood pressure; SD R-R, standard deviation of R-R intervals.

Values presented are mean (SD) and mean difference (95% CI), adjusted for age, sex, BMI percentile, current height-for-age, trunk tissue fat (%), parent education (college vs others), and race (white vs others).

Table IV.

Participant blood lipid, glucose, insulin, and HOMA-IR results by group status

Measure	Postinstitutionalized (n = 30), mean (SD)	Control (n = 90), mean (SD)	Adjusted difference (95% CI)	P value
Total cholesterol, mg/dL	169.8 (29.3)	155.4 (27.9)	15.2 (0.19-30.11)	.047
Total cholesterol, mmol/L	4.4 (0.8)	4.0 (0.7)		
LDL, mg/dL	92.0 (25.4)	82.3 (24.0)	14.4 (1.40-27.45)	.03
LDL, mmol/L	2.4 (0.7)	2.1 (0.6)		
HDL, mg/dL	59.7 (16.6)	57.3 (15.4)	-1.4 (-9.66 to -6.90)	.742
HDL, mmol/L	1.6 (0.4)	1.5 (0.4)		
Triglycerides, mg/dL	88.9 (39.3)	79.4 (34.7)	1.2 (1.01-1.54)	.048
Triglycerides, mmol/L	1 (0.4)	0.9 (0.4)		
Glucose, mg/dL	79.0 (8.7)	77.2 (8.7)	-0.7 (-5.76 to 4.36)	.785
Glucose, mmol/L	4.4 (0.5)	4.3 (0.5)		
Insulin, mU/L	7.8 (4.3)	5.0 (3.9)	1.6 (0.06-0.34)	.005
Insulin, mmol/L	54.2 (29.9)	34.7 (27.1)		
HOMA-IR	1.5 (0.9)	1.0 (0.8)	1.5 (1.10-2.12)	.01

HDL, high-density lipoprotein cholesterol; *LDL*, low-density lipoprotein cholesterol.

Values presented are mean (SD) and mean difference (95% CI), adjusted for age, sex, race (white vs others), BMI percentile, current height-for-age, parent education (college education or above), and trunk tissue fat (%).