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Associations of Early to Mid-Childhood Adiposity with Elevated Mid-Childhood Alanine Aminotransferase Levels in the Project Viva Cohort

Jennifer A. Woo Baidal, MD, MPH¹, Erin E. Elbel, BS¹, Joel E. Lavine, MD, PhD¹, Sheryl L. Rifas-Shiman, MPH², Matthew W. Gillman, MD, SM^{2,3}, Emily Oken, MD, MPH², and Elsie M. Taveras, MD, MPH⁴

¹Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Department of Pediatrics, Columbia University Medical Center, New York, NY

²Division of Chronic Disease Research Across the Lifecourse, Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA

³Dr. Gillman is now Director of the Environmental Influences on Child Health Outcomes (ECHO) Program, Office of the Director, National Institutes of Health, Bethesda, MD

⁴Division of General Academic Pediatrics, Department of Pediatrics, Massachusetts General Hospital, Boston, MA

Abstract

Objectives—To examine the longitudinal relationship of early to mid-childhood adiposity measures with mid-childhood alanine aminotransferase (ALT) levels.

Methods—We studied 635 children in the Project Viva cohort. Research staff measured weight, height, skinfolds thicknesses, and waist and hip circumferences at early (median 3.2 years) and mid-childhood (median 7.7 years) visits. At mid-childhood, we collected blood for ALT analysis. We used established sex-specific ALT cut-offs to define elevated ALT. In multivariable linear and logistic regression models, we assessed the association of adiposity measures from early to mid-childhood with mid-childhood ALT level, adjusting for confounders.

Results—Children were 48% female, 59% white, 21% black, 6% Hispanic/Latino, and 3% Asian. At early childhood, 29% had overweight/obesity and mean waist circumference was 51.5 (SD 3.8) cm. At mid-childhood, mean ALT was 20.3 (SD 7.3) units/liter and 23% had an elevated ALT. In multivariable-adjusted regression models, each additional 10 centimeters greater waist circumference at early childhood was associated with 1.99 (95% CI: 1.19, 3.33) higher odds of elevated ALT at mid-childhood. Greater increases from early to mid-childhood in BMI z-score,

Address correspondence to: Jennifer A. Woo Baidal, Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Department of Pediatrics, Columbia University Medical Center, New York, NY 10032 Tel: (212) 305-5903 Fax: (212) 342-5756. jw3286@cumc.columbia.edu.

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sum of subscapular and triceps skinfold thicknesses, waist circumference, and hip circumference were associated with higher ALT at mid-childhood.

Conclusions—In this prospective cohort, higher waist circumference at early childhood and greater increases in adiposity measures from early to mid-childhood were associated with higher ALT levels at mid-childhood.

Keywords

pediatric obesity; obesity; abdominal; non-alcoholic fatty liver disease

Childhood obesity is accompanied by myriad health complications, including nonalcoholic fatty liver disease (NAFLD). Mirroring the high prevalence of childhood obesity, NAFLD is now the most common cause of chronic liver disease in children.(1–3) A variety of disease phenotypes for NAFLD exist, including simple steatosis and steatohepatitis; the hallmark of each is hepatic steatosis (fat infiltration of liver cells) without alternative causes.(2) Long-term complications may include cirrhosis and hepatocellular carcinoma.

Approximately 10% of children and adolescents of all weight categories have NAFLD.(1,3) Cross-sectional studies show that overweight (sex-specific body mass index [BMI] 85th and <95th percentile for age), obesity (BMI 95th percentile), older age, Asian ancestry, Hispanic/Latino ethnicity, and male sex are risk factors for pediatric NAFLD.(1, 3–7) Given the high proportion of adolescents with NAFLD, early and mid-childhood could be key windows of opportunity to prevent development of disease. Yet scant prospective research exists on the relationship of adiposity early in childhood with pediatric NAFLD later in childhood. Population-based studies can shed light on these relationships to inform future efforts to prevent the development of NAFLD in children.

Some expert committees recommend use of serum alanine aminotransferase (ALT) levels to screen for NAFLD among at-risk children.(8, 9) Among children in the United States (US) ages 12–17 years, thresholds for serum ALT of 25.8 units/liter for males and 22.1 for females show 80–92% sensitivity and 79–85% specificity to detect pediatric NAFLD compared with magnetic resonance imaging and have been used in epidemiologic studies to estimate prevalence of suspected NAFLD.(1, 10) Continuous increases in serum ALT level have been linked with adverse health outcomes in adults of all BMI categories, including hepatocellular carcinoma risk, type 2 diabetes risk, and mortality.(11) In adolescents, cross-sectional studies have shown associations between ALT level, insulin resistance, and cardiometabolic risk, (12–14) but no studies have examined the relationship between ALT level and cardiometabolic health in younger children.

The overall goal of this research was to prospectively and longitudinally examine the relationship of child adiposity from early to mid-childhood with mid-childhood ALT levels. We hypothesized that higher adiposity during early childhood and greater increases in adiposity from early to mid-childhood would be associated with higher ALT levels in mid-childhood. As a secondary analysis, we additionally examined the cross-sectional relationship of ALT levels with cardiometabolic status at mid-childhood in this population-based cohort.

METHODS

We performed a study of children in Project Viva, an ongoing prospective pre-birth cohort study. Pregnant women were recruited from Atrius Harvard Vanguard Medical Associates, a multi-specialty group practice in eastern Massachusetts. Study recruitment and retention details are described elsewhere.(15) Mothers gave written informed consent at enrollment in pregnancy and at in-person visits in early (median age 3.2 years) and mid-childhood (median age 7.7 years), and children gave verbal assent at mid-childhood. The institutional review board of Harvard Pilgrim Health Care approved all study protocols.

Of the 2128 live singleton births in the cohort, 1708 remained enrolled and thus were eligible for a mid-childhood study visit and 1116 attended an in-person visit between ages 6 and 10 years. Of those, 635 had blood available for ALT analysis and form the study sample for this analysis. Characteristics of the study sample were similar to the excluded sample in terms of maternal age, education, parity, marital status, and pre-pregnancy BMI; household income; and child sex (data not shown). However, compared with children not included in this analysis, children in our study sample were more likely to be black, non-Hispanic (21% versus 15%) and less likely to be white, non-Hispanic (59% versus 66%).

Measurements

At early and mid-childhood outcomes, we measured height and weight of children using a calibrated stadiometer (Shorr Productions, Olney, MD) and scale (Seca model 881, Seca corporation, Hanover, MD). We calculated age- and sex-specific BMI z-scores and percentiles using CDC 2000 growth charts.(16) Trained research staff measured waist and hip circumferences using a Lefkin woven tape and subscapular and triceps skinfold thicknesses using Holtain calipers (Holtain LTD, Crosswell, United Kingdom). We calculated the sum (SS+TR) of the 2 thicknesses. Research assistants followed standardized techniques for measurements and participated in in-service training to ensure measurement validity (IJ Shorr, Shorr Productions, Olney, MD). (17) At the mid-childhood visit, we also measured total and trunk fat mass index (kg/m^2) by dual-energy X-ray absorptiometry (DXA) using Hologic model Discovery A (Hologic, Bedford, MA). Inter- and intra-rater measurement errors were well within published reference ranges for all measurements.(18, 19)

At the mid-childhood visit, phlebotomists collected blood samples from children. Samples were processed within 24 hours and frozen at -80°C until the time of analysis. We measured concentration of ALT by enzymatic assay on the Roche P Modular system using Roche reagents (Roche Diagnostics, Indianapolis, IN). This assay is approved by the Food and Drug Administration for clinical use and standardized across centers. The lowest detection limit of this assay is 4 U/L and the day-to-day imprecision values at concentrations of 42, 55 and 130 U/L are 4.4, 3.7 and 3.3%, respectively. We classified elevated ALT levels as >25.8 units/liter for males and >22.1 for females as in the SAFETY study and other studies of U.S. children age 12–17 years.(1, 10) As an additional analysis, we examined the relationship of adiposity measures with ALT levels using a threshold of >25 units/liter for both males and females as identified in the Canadian CALIPER study for children age 1 to <13 years.(20)

Research assistants measured systolic (SBP) and diastolic (DBP) blood pressures with a Dinamap (Critikon, Inc, Tampa, Florida) Pro 100 automated oscillometric recorder five times with each measure one minute apart. We calculated the average of 5 measurements. We collected blood from the antecubital vein in a vacutainer protected from sunlight and transported on ice for processing and storage within 24-hours. We measured plasma fasting insulin using an electrochemiluminescence immunoassay on the Roche E Modular system and fasting glucose enzymatically using Roche Diagnostics reagents (Roche Diagnostics, Indianapolis, IN). Using the HOMA-IR (fasting insulin [uU/mL] $\times$ fasting glucose [mg/dL]/405), we calculated insulin resistance. Triglycerides, total cholesterol, and HDL-cholesterol were measured enzymatically.

We calculated mid-childhood metabolic risk score as a mean of five sex- and cohort-specific z-scores for waist circumference, SBP, inverted HDL cholesterol, log-transformed triglycerides, and log-transformed HOMA-IR. Although no consistent definition of metabolic syndrome in young children exists, prior studies using similar scores show that higher risk scores indicate higher metabolic risk.(21–24)

At recruitment during pregnancy, we collected information including maternal age, education, parity, pre-pregnancy weight and height and marital status and household income. Child sex was extracted from delivery hospital records. At early childhood, we collected child race/ethnicity.

Statistical Analyses

We first examined the bivariate relationships of early childhood adiposity with other covariates and the main outcome. We then used linear and logistic regression models to assess the effect of adiposity measures at early childhood with ALT level at mid-childhood. We also examined the relationship between mid-childhood adiposity measures and changes in adiposity from early to mid-childhood with ALT level at mid-childhood. In multivariable models, we included only those covariates that were of *a priori* interest based on prior literature and our conceptual model. The fully-adjusted model included child age at the time of mid-childhood blood draw, sex, and race/ethnicity.

In secondary analyses, we assessed the relationship between mid-childhood ALT levels and mid-childhood metabolic risk score using linear regression models. We also examined the relationship between ALT and composite parts of the metabolic risk score at mid-childhood. We adjusted for covariates that could serve as confounders as above, and additionally for the potential intermediate of childhood BMI z-score. Because ALT levels can differ between girls and boys, we tested for effect modification based on child sex. We conducted all of the analyses using SAS version 9.4 (SAS Institute, Inc, Cary, North Carolina).

RESULTS

Table 1 shows parent and child characteristics of the 635 children included in this study. 48% were female, 59% were non-Hispanic white, 21% were non-Hispanic black, 6% Hispanic/Latino, and 3% were non-Hispanic Asian.

Table II shows early childhood adiposity measures, mid-childhood adiposity measures, and mid-childhood metabolic risk score and components by mid-childhood ALT category. At mid-childhood, mean (SD) ALT was 20.3 (7.3) units/liter. The proportion of children with elevated ALT levels were 23% overall, 20% for boys, and 27% for girls.

In Table 3, we present results from linear regression models testing our hypotheses that greater early childhood, mid-childhood, and changes from early to mid-childhood adiposity measures would be associated with higher ALT levels at mid-childhood. In unadjusted and child age- and sex-adjusted models, all early childhood adiposity measures were associated with mid-childhood ALT level, but only the association between waist circumference was statistically significant. In fully-adjusted models, each centimeter greater waist circumference at early childhood was associated with 0.24 units/liter (95% CI: 0.08, 0.40) higher mid-childhood ALT level.

In unadjusted models examining the cross-sectional relationship between adiposity and ALT level at mid-childhood, all adiposity measures (BMI z-score, waist circumference, hip circumference, sum of skinfolds thicknesses, waist-to-hip ratio, DXA total fat mass index, DXA total trunk fat mass index) were associated with higher ALT. Findings persisted in all models.

We found an association between change in adiposity measures from early to mid-childhood and mid-childhood ALT level for most adiposity measures (Table 3). Effect sizes and confidence intervals were similar in all models. In fully-adjusted models, each BMI z-score unit increase from early to mid-childhood was associated with 1.66 units/liter (95% CI: 0.89, 2.43) higher ALT level at mid-childhood. For sum of subscapular and triceps skinfolds thicknesses, each millimeter increase from early to mid-childhood was associated with 0.17 units/liter (0.09, 0.25) higher ALT level at mid-childhood. For each centimeter greater increase in waist and hip circumference from early to mid-childhood, we found 0.22 units/liter (95% CI: 0.13, 0.32) and 0.30 units/liter (0.20, 0.41) higher mid-childhood ALT level, respectively. For change in waist-to-hip ratio and mid-childhood ALT level, results included the null (Table 3).

We did not find evidence of effect modification by child sex in any models examining the relationships of early childhood, mid-childhood, or change from early to mid-childhood adiposity measures with mid-childhood ALT level (p-interaction > 0.1 for all models).

In unadjusted and multivariable-adjusted logistic regression models (Figure), we found that higher early childhood waist circumference; higher mid-childhood BMI z-score, skinfolds thickness, waist circumference, and hip circumference; and greater increases from early to mid-childhood in BMI z-score, skinfolds thickness, waist circumference, and hip circumference were associated with higher odds of elevated sex-specific ALT level at mid-childhood. In additional analyses using ALT thresholds from the Canadian CALIPER study, results were similar, but strengths of associations were greater (Table 4; available at www.jpeds.com). Early childhood BMI z-score, skinfolds thickness, hip circumference, and waist-to-hip ratio; mid-childhood waist-to-hip ratio; and change in waist-to-hip ratio from

early to mid-childhood with elevated ALT level at mid-childhood were not statistically significant.

We next investigated our secondary hypothesis that mid-childhood ALT level would be associated with metabolic risk at mid-childhood, and that this relationship would be independent of mid-childhood adiposity (Table 5; available at www.jpeds.com). Among the 527 children with complete data, mean metabolic risk z-score was 0.01 (SD 0.64). In models adjusted for child age and sex, higher ALT level was associated with higher metabolic risk score, systolic blood pressure, HOMA-IR, and fasting insulin. After additionally adjusting for child race/ethnicity, the relationships persisted: each higher ALT unit/liter was associated with 0.02 units (95% CI: 0.01, 0.02) higher metabolic risk score, 0.13 mm Hg (0.04, 0.22) higher SBP, 0.05 unit (0.03, 0.07) higher HOMA-IR, and 0.16 uU/mL (0.09, 0.23) higher fasting insulin. After adjusting for BMI z-score at mid-childhood, results for HOMA-IR and fasting insulin were attenuated but remained statistically significant. Adjusting for BMI z-score obliterated the associations of ALT level with metabolic risk score and SBP. In all models, relationships between ALT and DBP, triglycerides, total cholesterol, HDL cholesterol, and fasting glucose were not statistically significant.

DISCUSSION

In this prospective longitudinal cohort study, higher waist circumference at early childhood, higher adiposity measures at mid-childhood, and greater increases in adiposity measures from early to mid-childhood were risk factors for higher ALT levels at mid-childhood. We also found that higher ALT level was associated with higher insulin resistance and fasting insulin level at mid-childhood, with mid-childhood BMI z-score accounting for part, but not all, of these relationships. Our findings suggest that higher gains in adiposity from early to mid-childhood increase the likelihood of elevated ALT level at mid-childhood, and that adiposity only partially accounts for the link between higher ALT level and insulin resistance at mid-childhood.

Our study shows that increases in adiposity may have negative consequences on liver health, as measured by ALT levels, as young as mid-childhood. Other recent studies support a role of early life adiposity and nutrition in adverse liver health outcomes. In the Australian Raine cohort, 2 established childhood obesity risk factors, short duration of exclusive breastfeeding and maternal pre-pregnancy obesity, and concomitant adolescent obesity were identified as predictors for fatty liver disease defined by ultrasound measurement in adolescence.(25) Among children with biopsy-proven fatty liver disease, parental-report of another established childhood obesity risk factor –infant birth weight > 4 kg– was associated with greater severity of disease as measured by liver biopsy histology steatosis grade and presence of NASH.(26) Our results expand on these prior studies to show that early childhood adiposity may influence later childhood ALT levels in a population-based cohort. Furthermore, we showed that the adverse effects of early childhood adiposity on liver health can be found as early as mid-childhood, thus supporting the need to target early childhood for the prevention of obesity-related liver disease.

In our analyses of early childhood adiposity and mid-childhood ALT levels, we found that all measures of early childhood adiposity had direct associations with mid-childhood ALT levels, but only the relationship with waist circumference was statistically significant. Waist circumference is a measure of central adiposity, and cross-sectional studies of school-aged children and adolescents demonstrate that greater waist circumference is associated with cardiometabolic risk regardless of BMI category.(27, 28) Among adolescents, NAFLD is associated with hypertension, dyslipidemia, and insulin resistance independent of child adiposity.(29–31) Higher volume of visceral adipose tissue is correlated with central adiposity in adults, and visceral adipose tissue is correlated with liver inflammation and fibrosis.(32) Thus, it is possible that higher waist circumference in early childhood could presage central adiposity and its associated health risks later in life, but the relationship between waist circumference at early childhood and ALT level at mid-childhood has not been previously reported. Despite evidence for a relationship between child waist circumference and cardiometabolic risk, waist circumference is not uniformly measured as part of routine pediatric clinical care. Our findings support the use of waist circumference measurements in children as a clinical tool for assessing liver disease and cardiometabolic risk.

In our longitudinal analyses from early to mid-childhood, we found greater increases in all adiposity measures were associated with higher ALT levels at mid-childhood, with greater gains in BMI z-score most strongly associated with ALT elevation at mid-childhood. These results are similar to findings in other cohorts examining liver health outcomes in adults. In the Avon Longitudinal Study of Parents and Children, greater gains in weight-for-height between age 1 to 10 years were associated with higher odds of ALT level above 30 units/liter in adulthood.(33) In the Beijing Blood Pressure Cohort study, children with overweight or obesity early in adolescence (mean age 12 years) were more likely to have ultrasound-based diagnosis of steatosis and ALT elevation at adulthood, and those with larger gains in adiposity from adolescence to adulthood had highest odds of steatosis and ALT elevation. (34) We also found that higher ALT levels correlated with higher HOMA-IR and fasting insulin levels, and that associations were partially accounted for by mid-childhood BMI. Our findings concur with cross-sectional studies of adolescents that found a correlation between ALT level with insulin resistance, insulin levels, and metabolic risk. (12–14) We add to this literature to show that the liver complications of increasing adiposity can be apparent during mid-childhood.

Strengths of our study include the prospective nature of the design and its evaluation of risk factors during early and mid-childhood among a diverse cohort of children, providing support for the need to develop interventions prior to mid-childhood to prevent pediatric NAFLD. Our study has some limitations. Because this is a population-based cohort, we cannot report on liver imaging or liver tissue analysis, thus limiting our ability to determine grade and stage of liver disease. However, our findings are clinically meaningful as ALT levels are often recommended for NAFLD screening. Substantial evidence shows that higher ALT levels are linked to morbidity and mortality and our cross-sectional findings show that it is linked to insulin resistance even among a cohort of children with low metabolic risk scores during mid-childhood, supporting the role of ALT levels as an important health outcome measure in the general pediatric population. Also, not all children had all measures

for our secondary outcome of metabolic risk score and its components. Finally, we had small sample sizes of Asian and Hispanic children. These racial/ethnic groups are more likely to have NAFLD compared with non-Hispanic white or black children,⁽¹⁾ thus our effect estimates may underestimate the association of early and mid-childhood adiposity with circulating ALT levels.

In summary, we found that higher waist circumference during early childhood and increases in adiposity measures from early to mid-childhood were associated with higher odds of elevated ALT level during mid-childhood. Children with higher ALT at mid-childhood also had greater insulin resistance at mid-childhood, which was only partially accounted for by child BMI z-score. Our findings suggest that the time between early and mid-childhood is an important period in the prevention of obesity complications, including elevated ALT levels and insulin resistance. Early childhood should be targeted in future interventions to identify approaches to prevent pediatric obesity, liver disease, and related metabolic risk.

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Abbreviations

NAFLD	nonalcoholic fatty liver disease
ALT	alanine aminotransferase
BMI	body mass index

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Figure.

Associations of adiposity measures at early childhood and change from early to mid childhood with elevated ALT level at mid-childhood. Data from 635 children in Project Viva. Odds ratios for each increment of adiposity measure with elevated ALT level at mid-childhood adjusted for child age at mid-childhood visit, sex, and race/ethnicity.

Table 1

Parent and child characteristics according to early childhood body mass index categories. Data from 635 mother-child pairs participating in Project Viva.

	Overall	Early Childhood Body Mass Index Percentile		
		5 th to < 85 th	85 th to < 95 th	95 th
N	635	381	104	56
Family/Household characteristic				
Maternal age at enrollment, mean (SD), years	31.7 (5.6)	32.2 (5.6)	32.1 (5.1)	31.7 (5.3)
Education, college graduate, n (%)	408 (65)	265 (70)	74 (71)	27 (48)
Parity, nulliparous, n (%)	270 (43)	172 (45)	46 (44)	15 (27)
Marital status, married/cohabiting, n (%)	560 (89)	339 (89)	96 (93)	51 (91)
Household income, >\$70,000/y, n (%)	354 (61)	226 (63)	70 (73)	24 (45)
Pre-pregnancy BMI, mean (SD), kg/m ²	25.0 (5.3)	24.4 (4.9)	25.6 (5.4)	27.4 (6.0)
Child Characteristics				
Female, %	302 (48)	179 (47)	53 (51)	25 (45)
Age at early childhood visit, mean (SD), y	3.3 (0.4)	3.3 (0.3)	3.2 (0.2)	3.3 (0.5)
Age at mid-childhood visit, mean (SD), y	8.0 (0.8)	7.9 (0.8)	7.9 (0.7)	7.8 (0.7)
Race/ethnicity, n (%)				
Black, non-Hispanic	136 (21)	69 (18)	23 (22)	11 (20)
Hispanic	35 (6)	15 (4)	4 (4)	6 (11)
Asian, non-Hispanic	17 (3)	14 (4)	1 (1)	0 (0)
Other	73 (11)	41 (11)	12 (12)	6 (11)
White, non-Hispanic	373 (59)	242 (64)	64 (62)	33 (59)

Table 2

Early and mid-childhood adiposity according to mid-childhood alanine aminotransferase (ALT) level. Data from 635 children participating in Project Viva.

	Overall n=635	Normal ALT n=487	Elevated ALT n=148
	N (%) or Mean (SD)		
Early Childhood Adiposity			
BMI z-score, mean (SD)	0.51 (1.03)	0.49 (1.02)	0.59 (1.07)
BMI percentile, n (%)			
<5 th	13 (2.3)	11 (2.6)	2 (1.6)
5 th to <85 th	381 (68.8)	295 (69.1)	86 (67.7)
85 th to <95 th	104 (18.8)	80 (18.7)	24 (18.9)
95 th	56 (10.1)	41 (9.6)	15 (11.8)
Skinfolds, sum of subscapular and triceps, mean (SD), mm	16.7 (4.3)	16.5 (4.0)	17.3 (5.0)
Waist circumference, mean (SD), cm	51.5 (3.8)	51.3 (3.6)	52.2 (4.4)
Hip circumference, mean (SD), cm	56.9 (4.7)	56.8 (4.6)	57.3 (5.1)
Mid-Childhood Adiposity			
BMI z-score, mean (SD)	0.46 (1.02)	0.35 (1.02)	0.79 (0.97)
BMI percentile, n (%)			
<5 th	16 (2.6)	14 (2.9)	2 (1.4)
5 th to <85 th	432 (68.9)	343 (71.6)	89 (60.1)
85 th to <95 th	86 (13.7)	62 (12.9)	24 (16.2)
95 th	93 (14.8)	60 (12.5)	33 (22.3)
Skinfolds, sum of subscapular and triceps, mean (SD), mm	20.5 (10.5)	19.5 (9.7)	23.7 (12.1)
Waist circumference, mean (SD), cm	60.5 (9.1)	59.7 (8.6)	63.3 (10.0)
Hip circumference, mean (SD), cm	69.0 (8.4)	68.2 (7.9)	71.8 (9.2)
DXA total fat mass index, mean (SD), kg/m ²	4.5 (2.1)	4.3 (2.1)	5.1 (2.3)
DXA trunk fat mass index, mean (SD), kg/m ²	1.5 (1.0)	1.4 (0.9)	1.8 (1.1)
Mid-Childhood Metabolic Risk			
Metabolic Risk z-Score	0.01 (0.64)	−0.05 (0.62)	0.17 (0.69)
Diastolic blood pressure, mean (SD), mmHg	54.3 (5.5)	54.1 (5.4)	55.1 (5.9)
Systolic blood pressure, mean (SD), mmHg	94.7 (8.9)	94.2 (8.9)	96.4 (8.7)
Triglycerides, mean (SD), mg/dL	57.8 (24.7)	56.8 (23.3)	60.9 (28.7)
Total cholesterol, mean (SD), mg/dL	160.5 (27.1)	159.2 (27.5)	164.4 (25.7)
HDL cholesterol, mean (SD), mg/dL	57.2 (13.6)	57.2 (13.4)	57.0 (14.1)
HOMA-IR, mean (SD)	1.9 (1.8)	1.8 (1.7)	2.4 (2.1)
Fasting glucose, mean (SD), mg/dL	94.7 (15.0)	94.6 (14.9)	94.9 (15.3)
Fasting insulin, mean (SD), uU/mL	8.0 (6.5)	7.4 (5.9)	9.9 (7.8)

^aNormal ALT defined as < 22.1 units per liter for females and < 25.8 units per liter for males.

Table 3

Multivariable models showing associations of early and mid-childhood adiposity with mid-childhood alanine aminotransferase (ALT) levels. Data from 635 children.

	Age and sex-adjusted model β (95% CI) in ALT (units/liter) for each increment of adiposity measure	Covariate-adjusted model
Early childhood adiposity		
BMI z-score	0.47 (−0.13, 1.07)	0.50 (−0.11, 1.11)
SS+TR, mm	0.10 (−0.04, 0.25)	0.11 (−0.04, 0.26)
Waist circumference, cm	0.23 (0.07, 0.39)	0.24 (0.08, 0.40)
Hip circumference, cm	0.09 (−0.04, 0.22)	0.10 (−0.03, 0.23)
Waist-to-Hip Ratio	8.90 (−1.89, 19.69)	8.40 (−2.42, 19.22)
Mid-childhood adiposity		
BMI z-score	1.47 (0.92, 2.02)	1.54 (0.99, 2.10)
SS+TR, mm	0.12 (0.06, 0.18)	0.12 (0.07, 0.18)
Waist circumference, cm	0.17 (0.11, 0.24)	0.18 (0.11, 0.24)
Hip circumference, cm	0.19 (0.12, 0.27)	0.21 (0.13, 0.28)
Waist-to-Hip Ratio	16.03 (4.54, 27.52)	16.41 (4.96, 27.86)
DXA total fat mass index, kg/m ²	0.53 (0.24, 0.82)	0.54 (0.25, 0.84)
DXA trunk fat mass index, kg/m ²	1.17 (0.53, 1.81)	1.20 (0.56, 1.85)
Change from early to mid-childhood adiposity		
BMI z-score	1.59 (0.83, 2.35)	1.66 (0.89, 2.43)
SS+TR, mm	0.17 (0.09, 0.25)	0.17 (0.09, 0.25)
Waist circumference, cm	0.22 (0.13, 0.31)	0.22 (0.13, 0.32)
Hip circumference, cm	0.29 (0.19, 0.40)	0.30 (0.20, 0.41)
Waist-to-Hip Ratio	3.34 (−5.97, 12.64)	3.22 (−6.10, 12.53)

Bold indicates statistically significant models where 95% CI does not include zero

^a Age and sex-adjusted model: Adjusted for child age at time of mid-childhood blood draw and child sex

^b Covariate-adjusted model: Age and sex-adjusted model additionally adjusted for child race/ethnicity

Table 4

Associations of adiposity measures in early childhood and change from early to mid-childhood with elevated mid-childhood ALT levels.

	SAFETY ALT Thresholds ^a	CALIPER ALT Thresholds ^b
	Odds Ratio (95% CI)	
<i>Early childhood adiposity</i>		
BMI z-score	1.13 (0.93, 1.38)	1.23 (0.99, 1.52)
SS+TR, per 10 mm	1.46 (0.92, 2.34)	1.55 (0.94, 2.56)
Waist circumference, per 10 cm	1.99 (1.19, 3.33)	2.37 (1.37, 4.09)
Hip circumference, per 10 cm	1.36 (0.88, 2.09)	1.58 (1.00, 2.49)
<i>Change from early to mid-childhood adiposity</i>		
BMI z-score	1.58 (1.23, 2.03)	1.60 (1.22, 2.10)
SS+TR, per 10 mm	1.53 (1.20, 1.96)	1.66 (1.28, 2.15)
Waist circumference, per 10 cm	1.56 (1.16, 2.08)	1.70 (1.25, 2.32)
Hip circumference, per 10 cm	2.19 (1.53, 3.13)	2.32 (1.58, 3.39)

Adjusted for child age at mid-childhood blood draw, sex, and race/ethnicity

Bold indicates statistically significant models where 95% CI does not include one.

^aSAFETY ALT Thresholds: >22.1 units per liter for females and >25.8 units per liter for males

^bCALIPER ALT Thresholds: >25 units per liter for females and males

Table 5
Associations of alanine aminotransferase (ALT) level with metabolic risk markers at mid-childhood.

	N	Mean	SD	Age and sex-adjusted model ^a	Covariate-adjusted model ^b	BMIz-adjusted model ^c
Metabolic Risk z-Score	527	0.01	0.64	0.02 (0.01, 0.02)	0.02 (0.01, 0.02)	0.00 (0.00, 0.01)
Diastolic blood pressure, mmHg	626	54.3	5.52	0.02 (-0.04, 0.08)	0.02 (-0.04, 0.07)	0.00 (-0.06, 0.06)
Systolic blood pressure, mmHg	626	94.74	8.89	0.13 (0.04, 0.23)	0.13 (0.04, 0.22)	0.02 (-0.06, 0.11)
Triglycerides, mg/dL	581	57.8	24.71	0.19 (-0.09, 0.48)	0.18 (-0.11, 0.47)	0.02 (-0.27, 0.31)
Total cholesterol, mg/dL	582	160.45	27.14	0.32 (0.00, 0.63)	0.31 (0.00, 0.63)	0.30 (-0.02, 0.62)
HDL cholesterol, mg/dL	582	57.19	13.59	0.00 (-0.16, 0.15)	0.00 (-0.16, 0.16)	0.09 (-0.06, 0.25)
HOMA-IR	541	1.91	1.8	0.04 (0.02, 0.06)	0.05 (0.03, 0.07)	0.03 (0.01, 0.05)
Fasting glucose, mg/dL	546	94.65	15	0.16 (-0.01, 0.34)	0.16 (-0.02, 0.33)	0.12 (-0.06, 0.30)
Fasting insulin, uU/mL	587	8.02	6.47	0.16 (0.08, 0.23)	0.16 (0.09, 0.23)	0.08 (0.02, 0.15)

Bold indicates statistically significant models where 95% CI does not include zero

^a Age and sex-adjusted model: Adjusted for child age at time of mid-childhood blood draw and child sex

^b Covariate-adjusted model: Age and sex-adjusted model additionally adjusted for child race/ethnicity

^c BMIz-adjusted model: Covariate-adjusted model additionally adjusted for child BMI z-score at mid-childhood visit