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Childhood Hair Cortisol Concentration and Early Teen Cardiometabolic Outcomes

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Abstract

Objective: To examine associations of hair cortisol concentration (HCC) in mid-childhood and change in HCC from mid-childhood to early adolescence (ΔHCC) with early adolescent adiposity and cardiometabolic biomarker measures.

Methods: In Project Viva, a pre-birth cohort of mothers and children, we measured HCC in 599 white children in mid-childhood and in 426 of these participants in early adolescence. We used multivariable linear regression to examine associations of mid-childhood HCC and ΔHCC with BMI-for-age-and-sex z-score, waist circumference, waist-height ratio, dual X-ray absorptiometry total and trunk fat mass, a metabolic risk z-score, adiponectin, HOMA-IR, high-density lipoprotein, C-reactive protein, interleukin-6, leptin, and systolic blood pressure.

Results: Over a mean (SD) follow-up of 5.2 (0.8) years, we did not find associations of mid-childhood HCC with BMI-for-age-and-sex z-score (β=0.00 per 1-interquartile range of HCC, 95% confidence interval [CI]: −0.08, 0.07), waist circumference (β=−0.04cm, 95% CI: −0.83, 0.74), metabolic risk z-score (β=0.04, 95% CI: −0.03, 0.11), or other cardiometabolic measures except for an increase in log-transformed HOMA-IR (β=0.10, 95% CI: 0.04, 0.17). ΔHCC was not associated with any outcome measures.

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CONFLICTS OF INTEREST

The authors declared no conflict of interest.

Conclusions: We found that mid-childhood HCC was not associated with early adolescent adiposity or cardiometabolic biomarkers except for a slight increase in HOMA-IR.

Keywords

adiposity; children; cohort studies; hair cortisol concentration; metabolic syndrome

INTRODUCTION

Exposure to stress, including socioeconomic stress (1), violence (2), and others, has been associated with obesity and poor health in children. While several behavioral mechanisms (e.g. overnutrition, sedentary activity) may drive these associations, evidence for specific biological mechanisms linking stress with childhood cardiometabolic health is limited (3). One hypothesized biological mechanism is excess cortisol production, given that cortisol is released in response to stress (4), and that obesity and cardiometabolic risk are elevated in individuals with Cushing disease, which is defined by pathologically high cortisol levels (5). However, evidence for associations of cortisol (within the normal physiologic range) and cardiometabolic health in children is limited. The few studies that have examined associations of cortisol with adiposity (3) or other metabolic parameters (6, 7) in children have been inconsistent. Moreover, previous studies had small sample sizes, used one measure of blood, urinary, or salivary cortisol, which may not adequately represent long-term exposure (8), or were cross-sectional, raising questions regarding the directionality of observed associations.

We therefore examined associations of mid-childhood hair cortisol concentration (HCC), a measure of long-term circulating cortisol (9), with adiposity and cardiometabolic biomarker levels in early adolescence. We further examined how changes in HCC between mid-childhood and early adolescence (ΔHCC) were associated with these outcomes.

METHODS

Study Population.

Project Viva is a prospective pre-birth cohort that recruited 2,128 pregnant women carrying a singleton pregnancy during their initial obstetric care visit at Atrius Harvard Vanguard Medical Associates in eastern Massachusetts between 1999 and 2002 (10). Demographic, medical, lifestyle, and other health-related information on the 2,128 mother-child pairs enrolled in the study is collected via annual in-person interviews and/or questionnaires since baseline. Of 2,128 live singleton births, 1260 attended an in-person visit in mid-childhood (median age: 7.7 years; range: 6.6–10.7 years) or early adolescence (median age: 12.9 years; range: 11.9–16.6 years). We did not include non-White children because there were too few participants within strata of non-White racial and ethnic groups, and we did not want to pool data of participants of different races/ethnicities because of differences in hair texture and hair growth rate (11), which may make HCC measurements across groups incomparable. We excluded children who had taken inhaled or oral steroids within one month of the mid-childhood visit (n=40) because these medications may affect HCC measurements. After this exclusion, there were 599 children in the final analysis of mid-childhood HCC and

cardiometabolic outcomes. For ΔHCC, White children who provided hair samples at both the mid-childhood and early adolescent visit were eligible (n=456), and we excluded participants who had taken inhaled or oral steroids within one month of either visit (n=30), leaving n=426 children in this analysis. This study protocol was approved by the Institutional Review Board at Harvard Pilgrim Health Care. All mothers provided written informed consent and adolescents written assent.

HCC Measures.

We collected hair samples measuring at least 3cm in length from the posterior vertex region of the scalp of participants at the mid-childhood and early adolescent in-person research visits. Hair strands were cut as close as possible to the scalp, tied to identify the scalp end, and stored in a paper envelope away from light. For measurement of hair cortisol concentrations, lab personnel first washed the hair strands in isopropanol, and subsequently extracted cortisol using liquid chromatography tandem mass spectrometry (12). Based on an average hair growth rate of 1cm/month (13), 3cm of hair represents hair grown over approximately three months prior to collection, less the ~3 weeks of hair growth that has not yet emerged from the scalp. Only n=6 children in the mid-childhood HCC analyses (1%) and n=5 of those in ΔHCC analyses (1%) were undetectable; we kept these samples in our final analysis and assigned them a value of 0.01pg/mg, which was half of the lowest detectable HCC value.

Outcome Measures.

At the early adolescent in-person visit, we measured participants' weight using a calibrated Tanita scale (model TBF-300A; Tanita Corporation of America, Inc., Arlington Heights, IL) and height using a calibrated stadiometer (Shorr Productions, Olney, MD), from which we calculated BMI-for-age-and-sex z-scores (BMIZ) (14) and weight-height ratio. We measured waist circumference using a non-stretchable measuring tape (Hoechstmass Balzer GmbH, Sulzbach, Germany). We measured dual X-ray absorptiometry (DXA) using a Hologic model Discovery A (Hologic, Bedford, MA), from which we obtained total fat mass index (kg/m^2) and trunk fat mass index (kg/m^2).

We also collected an 8-hour fasting blood sample at the early adolescent visit. All samples were immediately refrigerated, processed within 24 hours, and stored at –80°C until time of analysis. These samples were used to measure high-density lipoprotein (HDL), triglycerides, insulin, leptin, adiponectin, C-reactive protein (CRP), and interleukin-6 (IL-6) in plasma. Systolic blood pressure (SBP) was measured five times using biannually-calibrated automated oscillometric monitors (Dinamap Pro100, Tampa, Florida); these five measures were averaged to calculate mean SBP. We created a metabolic risk z-score (METZ) using waist circumference, SBP, HDL cholesterol, HOMA-IR, and triglycerides, as described previously (15).

Covariate Data.

Mothers reported their age, educational attainment, household income, pre-pregnancy weight, height, and smoking history via self-administered questionnaire and interview at recruitment. We extracted data on infant birth date and sex from hospital medical records.

We calculated gestational age by subtracting the date of the last menstrual period from the date of delivery. If gestational age according to second-trimester ultrasound scan differed from that according to the last menstrual period by more than ten days, we used the ultrasound result to determine gestational age. We collected infant birth weight from hospital medical records, and calculated birth weight-for-sex-and-gestational age z-scores using national reference data (16). Child waist circumference, weight, and height were measured at the early childhood visit (median age: 3.1 years; range: 2.9–6.0 years) using methods described above; these were used to calculate early childhood BMIZ and waist-height ratio. At the mid-childhood visit, mothers reported children's secondhand smoke exposure (at home or outside of home) and oral or inhaled steroid use via questionnaire and interviews. At the mid-childhood visit, mothers reported children's pubertal development via the Pubertal Development Scale, which is moderately correlated with physician Tanner staging (17, 18).

Statistical Analysis.

To improve normality, we natural log-transformed HCC, HOMA-IR, CRP, IL-6, and leptin values. In our primary analysis, we used linear regression to estimate associations of mid-childhood HCC (in quartiles and continuously) with early adolescent adiposity measures and cardiometabolic biomarker levels. These models adjusted for maternal age at enrollment, maternal education, pre-pregnancy BMI, maternal smoking during pregnancy, household income, child age, child sex, birthweight-for-sex-and-gestational age z-score, secondhand smoke exposure, and mid-childhood pubertal development score. For BMIZ, waist circumference, and waist-height ratio, we adjusted for the respective adiposity measure from the early childhood visit (DXA measures and the blood biomarkers were not measured at the early childhood visit). We chose to adjust for early childhood adiposity measures instead of mid-childhood adiposity measures because it is possible that mid-childhood HCC could affect mid-childhood adiposity, which could partially block the association of mid-childhood HCC with early adolescent adiposity. All analyses of metabolic biomarkers were also adjusted for early childhood BMIZ. In sensitivity analyses, we repeated this primary analysis but excluded children who used oral or inhaled steroids in the year before hair collection. In another sensitivity analysis, we used multinomial logistic regression to examine associations of mid-childhood HCC on the odds of having obesity (BMI $\geq 95^{th}$ percentile) and on the odds of having overweight (BMI in 85^{th} to 95^{th} percentile) in early adolescence compared to having normal weight (BMI $< 85^{th}$ percentile). We used multiple imputation to impute values of missing data for all covariates in all analyses by imputing 50 values for each missing observation and then combining the multivariable modeling estimates using PROC MIANALYZE. We did not impute any HCC values or outcomes. We tested for interaction by child sex in our primary analyses, but because there were no significant interactions, we present results for associations in males and females combined.

We conducted a secondary analysis examining quartiles and continuous ΔHCC with the same outcomes and covariates as in our primary analysis. We conducted another secondary analysis where we formed quartiles of mid-childhood and early adolescent HCC and then examined associations with early adolescent outcomes according to the number of times

participants were in the top quartile of HCC (i.e. never [reference], only in mid-childhood, only in early adolescence, or in both mid-childhood and early adolescence).

We conducted two exploratory analyses where we 1) examined cross-sectional associations between mid-childhood HCC and mid-childhood adiposity measures, and 2) examined associations of mid-childhood adiposity measures with early adolescent HCC. We did these to explore whether reverse causation may have affected results of previous cross-sectional studies that found strong associations of HCC with adiposity in children. All secondary and exploratory analyses were conducted in the imputed dataset.

We calculated 2-sided 95% confidence intervals (CI) for all statistical tests. We performed all analyses using SAS version 9.4 (Cary, NC).

RESULTS

The median mid-childhood HCC was 1.0pg/mg (interquartile range, IQR: 0.5, 2.4), and the median ΔHCC was an increase of 0.8pg/mg (−0.5, 2.6). Compared to participants in the lowest quartile of mid-childhood HCC, those in the highest quartile were more likely to be male and to have been exposed to secondhand smoke. They were also more likely to have a mother who did not graduate from college and who smoked during pregnancy (Table 1). We compared characteristics of the 599 White children in our main analysis to the 745 White Project Viva participants who were excluded and found that excluded participants were less likely to have college-educated mothers, live in homes with annual income exceeding $70,000, and more likely to have mothers who smoked during pregnancy (Table S1). There were very few missing covariates in the analytic sample (<5% missing for all covariates); thus, the distributions of imputed and non-imputed covariates were nearly identical for all covariates (Table S2).

We did not observe any associations between mid-childhood HCC and early adolescent BMIZ (β=0.00 per 1-IQR increase in mid-childhood HCC, 95% CI: −0.08, 0.07), waist circumference (β=−0.04cm, 95% CI: −0.83, 0.74), waist-height ratio (β=0.02, 95% CI: −0.03, 0.07), or either DXA measure of fat mass (Table 2). We similarly did not observe associations of mid-childhood HCC with early adolescent obesity or overweight (Table S3). We did not observe associations of mid-childhood HCC with METZ or other cardiometabolic biomarkers in early adolescence except for an increase in log-transformed HOMA-IR (β=0.10, 95% CI: 0.04, 0.17). When we modeled HCC in quartiles, we observed similar results for all outcomes, though the CI for HOMA-IR included the null (β=0.19 for highest vs. lowest quartile, 95% CI: −0.01, 0.38). Results were similar when we excluded children who had taken steroids in the year before hair collection (Table S4). ΔHCC between mid-childhood and early adolescence was not associated with any adiposity or cardiometabolic biomarker measure in early adolescence (Table 3). Having HCC in the top quartile in mid-childhood alone, early adolescence alone, or in both periods was not associated with any outcomes compared to those who were never in the top quartile of HCC. One exception was for HOMA-IR, which was elevated in those who were in the top quartile of mid-childhood HCC alone (β=0.27, 95% CI: 0.07, 0.47), but not for those with HCC in the top quartile in early adolescence or in both periods (Table 4).

Because previous cross-sectional studies have reported strong associations of HCC with adiposity in children (19), we reexamined our primary analyses using adiposity measures and HCC from the mid-childhood visit. We found several stronger associations compared to when we examined HCC and adiposity measures prospectively (Table S5). However, we did not observe associations of early childhood adiposity measures with mid-childhood HCC or of mid-childhood adiposity measures with early adolescent HCC (Table S6).

DISCUSSION

Mid-childhood HCC was associated with greater insulin resistance but not with other early adolescent adiposity measures or cardiometabolic biomarker concentrations. Change in HCC from mid-childhood to early adolescence was not associated with adiposity or cardiometabolic biomarkers.

To our knowledge, this study is the first to prospectively examine associations of HCC with measures of cardiometabolic health in children. The association between childhood HCC and early adolescent HOMA-IR implies a potential role of cortisol in development of insulin resistance in children. Our finding is consistent with data showing that glucocorticoids promote gluconeogenesis and inhibit glucose uptake in muscle and adipose tissue (20). Moreover, insulin resistance is a hallmark of Cushing's disease (5). Our findings are also consistent with studies observing higher glucocorticoid concentrations in insulin-sensitive versus insulin-resistant children (21). However, this observation could be due to chance given the number of tests we conducted. The fact that we did not observe an association among those who had HCC in the top quartile in both mid-childhood and early adolescence compared to those who never had HCC in the top quartile also underlines this possibility. We would expect at least a slight association with HOMA-IR in this group if there was a meaningful role of cortisol in insulin resistance, although the referent group in this analysis, which included participants with HCC in the first, second and third quartiles, could have reduced the contrast between groups. Replication of this finding is thus warranted, especially in children of other racial/ethnic groups.

We did not observe associations between HCC and adiposity in early adolescence. Results from previous cross-sectional studies have been inconsistent, with one finding no association between child HCC and adiposity (22), another finding a weak association between HCC and BMI in girls only (23), and one finding a strong association between childhood HCC and odds of obesity (OR=9.4 for highest vs. lowest quintile) (19). To explore whether results from this last study, conducted in the Generation R cohort, could be explained by reverse causality due to simultaneous measurement of HCC and adiposity, we conducted analyses that similarly examined HCC and adiposity measures cross-sectionally. We found some stronger results in the cross-sectional analysis compared to the analysis where HCC and adiposity were examined prospectively (which was likely the more valid one). However, we did not find any associations of early childhood adiposity with mid-childhood HCC, or of mid-childhood adiposity with early adolescent HCC. It therefore appears unlikely that reverse causation alone could explain the very strong results observed in the Generation R study. A prospective investigation is nevertheless important for estimating the effect of HCC on adiposity in children, and the fact that our cross-sectional results were stronger than the

prospective ones suggests some bias that may partially explain the results in the Generation R study. It is also possible that there are differences between Generation R and Project Viva that could explain the different associations, though both cohorts collected hair samples around the same age, used the same method for HCC analysis, and observed similar median HCC.

There are several possible explanations for the lack of association of HCC with adiposity in early adolescence. First, although HCC is elevated in individuals with Cushing's disease (8), HCC may not be a highly accurate measure of longstanding systemic cortisol concentration within the physiologic range. Future validation studies of HCC are thus necessary. Second, it is possible that well-documented relationships between childhood stress and obesity are mediated by factors unrelated to cortisol secretion, such as child self-regulation and health behaviors (3). Third, it is possible that high cortisol in childhood does not have an effect on adiposity and cardiometabolic health until adulthood. This has been suggested for other biological processes, such as inflammation (24). Lastly, participants in this analysis (i.e. white children, most of whom lived in high-income households and had health insurance) are likely healthier and less stressed than children in the general US population. These characteristics may have prevented us from examining large contrasts in stress-related HCC, which may have reduced our power to detect associations (although it may have the benefit of minimizing confounding). If this study were repeated in a population with a wider distribution of HCC (or stress), more prominent associations could possibly be observed.

This study has several strengths (e.g. prospective data collection, HCC measurements at two times, adjustment for many confounders etc.), but also has limitations. First, we included only white participants of high socioeconomic status, which may reduce the generalizability of our findings. Second, we did not have duplicate hair samples, and so could not assess the intra-assay coefficient of variation (%CV) of HCC. However, the intra-assay %CV was <10% in other studies using this method (25). Last, we lacked information on hair color, texture, and frequency of washing, and so could not standardize HCC to these variables. However, most studies have not reported associations between hair characteristics with HCC in children of the same race/ethnicity (26), suggesting an immaterial impact on our results.

In summary, HCC in mid-childhood was associated with HOMA-IR but not with other adiposity or cardiometabolic outcomes in early adolescence. Replication of this study in other prospective cohorts is necessary to confirm these findings, as is further exploration of mechanisms (biological or otherwise) through which childhood stress is associated with adiposity and chronic disease risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BMIZ	Body mass index-for-age-and-sex z-scores
CI	confidence interval
CV	coefficient of variation
DXA	dual X-ray absorptiometry
HCC	hair cortisol concentration
HDL	high-density lipoprotein
IQR	interquartile range
METZ	metabolic risk z-score
SBP	systolic blood pressure

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Table 1.

Characteristics[a] of White Project Viva Participants by Quartile of Mid-Childhood Hair Cortisol Concentration

Characteristic	Q1 (n=149)	Q2 (n=151)	Q3 (n=149)	Q4 (n=150)
Female (%)	64	56	52	45
Parental Characteristics				
Maternal age at enrollment (years)	33.4 (4.0)	33.5 (4.2)	33.3 (4.4)	33.8 (4.4)
Maternal pre-pregnancy BMI (kg/m^2)	23.7 (4.1)	23.9 (4.7)	23.8 (4.3)	24.8 (4.7)
Yearly household income (% ≥ $70,000)	75	71	75	74
Mother's education (% college graduate)	85	83	78	79
Mother smoked during pregnancy (%)	7	7	6	12
Early Life Characteristics				
Birthweight-for-sex-and-gestational age z-score	0.49 (0.84)	0.36 (0.93)	0.22 (0.88)	0.26 (1.05)
Gestational age (weeks)	39.8 (1.9)	39.7 (1.5)	39.7 (1.6)	39.7 (1.3)
Mid-childhood Characteristics				
Mid-childhood HCC[b] (pg/mg)	0.3 (0.1, 0.4)	0.7 (0.6, 0.8)	1.5 (1.2, 1.9)	5.7 (3.6, 12.8)
Age at mid-childhood hair collection (years)	7.8 (0.8)	7.8 (0.7)	7.9 (0.7)	7.9 (0.8)
Secondhand smoke exposure	7	10	7	14
Pubertal development score	1.1 (0.3)	1.1 (0.2)	1.1 (0.3)	1.1 (0.3)
Early Adolescent Characteristics				
Adolescent HCC[b]	2.0 (1.0, 3.7)	2.0 (0.8, 3.7)	2.2 (1.2, 4.2)	2.6 (1.3, 5.1)
Age at early adolescent hair collection (years)	13.1 (0.8)	13.0 (0.8)	13.0 (0.7)	13.2 (1.0)
BMI (kg/m^2)	20.3 (3.4)	19.6 (3.1)	20.4 (3.7)	20.7 (4.3)
BMI-for-age-and-sex z-score	0.27 (0.95)	0.12 (0.98)	0.34 (0.99)	0.37 (1.07)
Waist circumference (cm)	71.8 (9.2)	70.5 (8.5)	73.2 (10.8)	73.0 (11.9)
Waist-height ratio	0.45 (0.05)	0.44 (0.05)	0.46 (0.06)	0.46 (0.07)
DXA total fat mass (kg/m^2)	6.1 (2.5)	5.7 (2.2)	6.3 (2.6)	6.3 (2.8)
DXA trunk fat index (kg/m^2)	2.3 (1.2)	2.1 (1.0)	2.4 (1.2)	2.4 (1.4)
Metabolic risk z-score	−0.04 (0.59)	−0.12 (0.52)	0.07 (0.59)	0.04 (0.68)
Systolic blood pressure (mm Hg)	106.1 (9.4)	107.3 (8.9)	106.5 (9.9)	106.5 (9.7)

Characteristic	Q1 (n=149)	Q2 (n=151)	Q3 (n=149)	Q4 (n=150)
HOMA-IR[b]	2.5 (1.9, 3.7)	2.4 (1.6, 3.2)	2.8 (1.9, 4.0)	3.3 (2.0, 4.2)
Fasting insulin (μIU/mL)[b]	11.6 (8.6, 16.7)	11.2 (7.9, 15.5)	13.9 (9.8, 19.9)	15.1 (9.2, 18.6)
HDL cholesterol (mg/dL)[b]	54.0 (48.2, 61.2)	56.4 (46.9, 64.9)	52.5 (45.2, 59.4)	56.0 (47.7, 65.1)
Triglycerides (mg/dL)	64.0 (47.0, 86.0)	65.0 (51.5, 90.5)	72.0 (52.0, 92.0)	65.0 (48.0, 88.5)
C-reactive protein (mg/L)[b]	0.2 (0.1, 0.5)	0.3 (0.2, 0.5)	0.3 (0.2, 1.0)	0.2 (0.1, 0.8)
Interleukin-6 (pg/mL)[b]	0.8 (0.6, 1.0)	0.8 (0.7, 1.1)	0.8 (0.6, 1.2)	0.8 (0.6, 1.2)
Adiponectin (μg/mL)[b]	6.2 (4.8, 8.7)	6.4 (4.9, 8.6)	6.1 (4.3, 8.2)	5.9 (4.4, 8.1)
Leptin (ng/mL)[b]	6.5 (3.5, 12.7)	5.7 (3.3, 10.7)	7.2 (3.0, 15.3)	7.8 (3.0, 16.1)

[a] Mean (SD) or % presented unless otherwise stated

[b] Median and interquartile range presented

Table 2.

Associations Between Mid-Child Hair Cortisol Concentrations[a] and Early Teen Measures of Adiposity in White Participants

	Adjusted β (95% CI)[b]				
	Q1	**Q2**	**Q3**	**Q4**	**Continuous[c]**
BMI-for-age-and-sex z-score (n=491)[d]	0.00 (ref)	−0.22 (−0.43, −0.02)	−0.03 (−0.25, 0.18)	−0.10 (−0.31, 0.11)	0.00 (−0.08, 0.07)
Waist circumference, cm (n=493)[e]	0.00 (ref)	−1.83 (−4.02, 0.35)	0.82 (−1.44, 3.08)	−0.68 (−2.91, 1.56)	−0.04 (−0.83, 0.74)
Waist-height ratio (n=491)[f]	0.00 (ref)	−0.007 (−0.020, 0.007)	0.011 (−0.003, 0.024)	0.002 (−0.011, 0.016)	0.002 (−0.003, 0.007)
DXA total fat mass, kg/m^2 (n=371)	0.00 (ref)	−0.39 (−1.07, 0.29)	0.25 (−0.47, 0.96)	0.27 (−0.43, 0.96)	0.10 (−0.15, 0.35)
DXA truncal fat mass index, kg/m^2 (n=371)	0.00 (ref)	−0.18 (−0.50, 0.13)	0.11 (−0.22, 0.45)	0.09 (−0.24, 0.42)	0.04 (−0.08, 0.16)
Metabolic risk z-score (n=290)[d]	0.00 (ref)	−0.06 (−0.25, 0.12)	0.09 (−0.11, 0.29)	0.04 (−0.15, 0.24)	0.04 (−0.03, 0.11)
Adiponectin, (μg/ml) (n=327)[d]	0.00 (ref)	0.00 (−0.84, 0.84)	−0.58 (−1.46, 0.30)	−0.31 (−1.16, 0.55)	−0.11 (−0.40, 0.19)
HOMA-IR (n=291)[a,d]	0.00 (ref)	−0.08 (−0.27, 0.10)	0.04 (−0.16, 0.24)	0.19 (−0.01, 0.38)	0.10 (0.04, 0.17)
HDL, mg/dL (n=327)[d]	0.00 (ref)	2.79 (−1.24, 6.82)	0.23 (−4.00, 4.45)	3.33 (−0.78, 7.45)	0.50 (−0.93, 1.93)
CRP, mg/L (n=317)[a,d]	0.00 (ref)	0.12 (−0.22, 0.45)	0.36 (0.01, 0.71)	0.10 (−0.24, 0.43)	−0.02 (−0.14, 0.10)
IL-6, pg/mL (n=327)[a,d]	0.00 (ref)	0.06 (−0.14, 0.26)	0.09 (−0.12, 0.30)	0.02 (−0.19, 0.22)	0.00 (−0.07, 0.07)
Leptin, ng/mL (n=327)[a,d]	0.00 (ref)	−0.06 (−0.32, 0.21)	0.04 (−0.24, 0.31)	0.10 (−0.17, 0.37)	0.03 (−0.06, 0.12)
Systolic blood pressure, mm Hg (n=490)[d]	0.00 (ref)	0.67 (−1.64, 2.99)	−0.26 (−2.66, 2.14)	−0.78 (−3.15, 1.60)	0.15 (−0.68, 0.98)

[a] Natural log-transformed

[b] All adjusted for maternal age at enrollment (years, continuous), maternal education (college graduate [ref], not a college graduate), pre-pregnancy BMI (kg/m2, continuous), maternal smoking during pregnancy (yes, no [ref]), household income (<$70,000 [ref], ≥$70,000), child age (continuous, years), child sex (female [ref] vs. male), birthweight-for-sex-and-gestational age z-score (continuous), secondhand smoke exposure (no [ref], yes), mid-childhood pubertal development score (continuous)

[c] Per 1-interquartile range increase in natural log-transformed mid-childhood HCC

[d] Additionally adjusted for early childhood BMI z-score

[e] Additionally adjusted for early childhood waist circumference

[f] Additionally adjusted for early childhood waist-height ratio

Table 3.

Associations Between Change in Hair Cortisol Concentrations from Mid-Childhood to Early Adolescence[a] and Early Teen Measures of Adiposity in White Participants

	Adjusted β (95% CI)[b]				
	Q1	**Q2**	**Q3**	**Q4**	**Continuous[b]**
BMI z-score (n=424)[d]	0.00 (ref)	0.11 (−0.11, 0.34)	0.06 (−0.17, 0.29)	0.03 (−0.20, 0.26)	−0.03 (−0.12, 0.06)
Waist circumference, cm (n=426)[e]	0.00 (ref)	1.49 (−0.89, 3.88)	0.71 (−1.70, 3.11)	−0.31 (−2.74, 2.12)	−0.36 (−1.33, 0.60)
Waist-height ratio (n=424)[f]	0.00 (ref)	0.007 (−0.007, 0.022)	−0.001 (−0.016, 0.013)	−0.005 (−0.020, 0.010)	−0.004 (−0.010, 0.002)
DXA total fat mass, kg/m^2 (n=320)[c]	0.00 (ref)	0.62 (−0.11, 1.36)	0.20 (−0.55, 0.94)	0.05 (−0.71, 0.81)	−0.02 (−0.33, 0.29)
DXA truncal fat mass index, kg/m^2 (n=320)[c]	0.00 (ref)	0.34 (0.00, 0.68)	0.16 (−0.19, 0.50)	0.08 (−0.27, 0.44)	0.02 (−0.13, 0.16)
Metabolic risk z-score (n=249)[d]	0.00 (ref)	0.09 (−0.10, 0.29)	0.02 (−0.18, 0.23)	0.06 (−0.14, 0.26)	0.04 (−0.04, 0.11)
Adiponectin, μg/mL (n=279)[d]	0.00 (ref)	−0.82 (−1.70, 0.07)	−0.13 (−1.06, 0.80)	−0.22 (−1.13, 0.69)	−0.02 (−0.39, 0.34)
HOMA-IR (n=249)[a,d]	0.00 (ref)	−0.02 (−0.22, 0.18)	−0.13 (−0.34, 0.08)	−0.11 (−0.31, 0.09)	−0.04 (−0.12, 0.04)
HDL, mg/dL (n=279)[d]	0.00 (ref)	−3.47 (−7.53, 0.60)	−3.02 (−7.28, 1.23)	−0.65 (−4.83, 3.52)	−0.39 (−2.06, 1.28)
CRP, mg/L (n=269)[a,d]	0.00 (ref)	0.17 (−0.17, 0.52)	0.28 (−0.07, 0.64)	0.17 (−0.18, 0.52)	0.04 (−0.10, 0.18)
IL-6, pg/mL (n=279)[a,d]	0.00 (ref)	0.16 (−0.04, 0.37)	0.05 (−0.17, 0.26)	−0.06 (−0.27, 0.16)	−0.03 (−0.11, 0.06)
Leptin, ng/mL (n=279)[a,d]	0.00 (ref)	0.04 (−0.24, 0.31)	−0.18 (−0.46, 0.11)	0.00 (−0.28, 0.28)	−0.01 (−0.13, 0.10)
Systolic blood pressure, mm Hg (n=425)[d]	0.00 (ref)	1.61 (−0.90, 4.13)	0.64 (−1.89, 3.17)	0.52 (−2.03, 3.08)	0.04 (−0.98, 1.05)

[a] Natural log-transformed

[b] All adjusted for maternal age at enrollment (years, continuous), maternal education (college graduate [ref], not a college graduate), pre-pregnancy BMI (kg/m2, continuous), maternal smoking during pregnancy (yes, no [ref]), household income (<$70,000 [ref], ≥$70,000), child age (continuous, years), child sex (female [ref] vs. male), birthweight-for-sex-and-gestational age z-score (continuous), secondhand smoke exposure (no [ref], yes), mid-childhood pubertal development score (continuous)

[c] Per 1-interquartile range increase in natural log-transformed HCC

[d] Additionally adjusted for early childhood BMI z-score

[e] Additionally adjusted for early childhood waist circumference

[f] Additionally adjusted for early childhood waist-height ratio

Table 4.

Associations of Being in the Top Quartile of Hair Cortisol Concentration[a] with Early Teen Adiposity and Cardiometabolic Measures

	Adjusted β (95% CI)[b]			
Outcome	**Never in top quartile (N=246)**	**Top quartile in mid-childhood only (N=74)**	**Top quartile in early adolescence only (N=72)**	**Top quartile in mid-childhood and early adolescence (N=34)**
BMI z-score (n=424)[c]	0.00 (ref)	0.09 (−0.13, 0.31)	0.10 (−0.13, 0.33)	−0.08 (−0.39, 0.22)
Waist circumference, cm (n=426)[d]	0.00 (ref)	0.77 (−1.59, 3.12)	0.23 (−2.13, 2.59)	−1.57 (−4.78, 1.63)
Waist-height ratio (n=424)[e]	0.00 (ref)	0.009 (−0.006, 0.023)	0.000 (−0.014, 0.015)	−0.008 (−0.028, 0.011)
DXA total fat mass, kg/m^2 (n=320)	0.00 (ref)	0.64 (−0.08, 1.37)	0.06 (−0.70, 0.82)	0.17 (−0.93, 1.27)
DXA truncal fat mass index, kg/m^2 (n=320)	0.00 (ref)	0.28 (−0.05, 0.62)	0.09 (−0.26, 0.44)	0.06 (−0.45, 0.57)
Metabolic risk z-score (n=249)[c]	0.00 (ref)	0.06 (−0.13, 0.26)	0.03 (−0.17, 0.23)	−0.04 (−0.33, 0.25)
Adiponectin, μg/mL (n=279)[c]	0.00 (ref)	−0.07 (−0.95, 0.81)	0.58 (−0.32, 1.49)	0.12 (−1.17, 1.41)
HOMA-IR (n=249)[a,c]	0.00 (ref)	0.27 (0.07, 0.47)	−0.05 (−0.25, 0.16)	0.01 (−0.28, 0.31)
HDL, mg/dL (n=279)[c]	0.00 (ref)	1.19 (−2.83, 5.20)	0.40 (−3.74, 4.54)	3.48 (−2.43, 9.40)
CRP, mg/L (n=269)[a,c]	0.00 (ref)	−0.10 (−0.43, 0.24)	−0.10 (−0.45, 0.25)	−0.31 (−0.80, 0.18)
IL-6, pg/mL (n=279)[a,c]	0.00 (ref)	−0.02 (−0.22, 0.19)	−0.11 (−0.32, 0.11)	−0.09 (−0.40, 0.21)
Leptin, ng/mL (n=279)[a,c]	0.00 (ref)	0.23 (−0.04, 0.50)	−0.04 (−0.32, 0.24)	0.03 (−0.36, 0.43)
Systolic blood pressure, mm Hg (n=425)[c]	0.00 (ref)	−0.52 (−2.99, 1.94)	−0.06 (−2.53, 2.41)	−1.43 (−4.79, 1.93)

[a] Natural log-transformed

[b] All adjusted for maternal age at enrollment (years, continuous), maternal education (college graduate [ref], not a college graduate), pre-pregnancy BMI (kg/m2, continuous), maternal smoking during pregnancy (yes, no [ref]), household income (<$70,000 [ref], ≥$70,000), child age (continuous, years), child sex (female [ref] vs. male), birthweight-for-sex-and-gestational age z-score (continuous), secondhand smoke exposure (no [ref], yes), mid-childhood pubertal development score (continuous)

[c] Additionally adjusted for early childhood BMI z-score

[d] Additionally adjusted for early childhood waist circumference

[e] Additionally adjusted for early childhood waist-height ratio