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Metabolic trajectories across early adolescence: differences by sex, weight, pubertal status, and race/ethnicity

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Abstract

Background: Biomarkers of cardiovascular and metabolic risk track from adolescence into adulthood, therefore characterising the direction and magnitude of these changes is an important first step to identifying health trajectories that presage future disease risk.

Aim: To characterise changes in metabolic biomarkers across early adolescence in a multi-ethnic cohort.

Subjects & methods: Among 891 participants in Project Viva we estimated changes in insulin resistance (HOMA-IR), adipokines, lipids, and SBP between ages 6–10 years and 11–16 years. Next, we used multivariable linear regression to examine associations of sex, baseline overweight/obesity, baseline pubertal status, and race/ethnicity with change in the biomarkers during follow-up.

Results: Boys exhibited a larger decrement in adiponectin (−0.66 [95% CI: −1.14, −0.18)] ng/mL) and a greater increase in SBP (3.20 [2.10, 4.30] mmHg) than girls. Overweight/obese participants experienced larger increases in HOMA-IR, leptin, and triglycerides; and a steeper decrement in HDL. Pubertal youth showed larger decrements in total and LDL cholesterol than their pre-pubertal counterparts. In comparison to White participants, Black youth experienced a larger magnitude of increase in HOMA-IR, and Hispanic youth exhibited larger decrements in adiponectin and HDL.

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Conclusions: Change in metabolic biomarkers across early adolescence differed by sex, weight status, pubertal status, and race/ethnicity. Some of the metabolic changes may reflect normal physiological changes of puberty, while others may presage future disease risk. Future studies are warranted to link metabolic changes during adolescence to long-term health.

Keywords

puberty; obesity; insulin resistance; triglycerides; inflammation; adiponectin; insulin; adolescence

BACKGROUND

Adolescence is a time of change. Activation of the reproductive axis coincides with exacerbation of many metabolic risk factors, including increased blood pressure (Spagnolo et al. 2013; Hardy et al. 2015), adverse changes to adipokines (Ahmed et al. 1999; Bottner et al. 2004), dips in lipids (Chiang et al. 1989; Morrison et al. 2003; Dai et al. 2009), and emergence of insulin resistance (Moran et al. 1999; Goran and Gower 2001). Given that many biomarkers of cardiovascular and metabolic risk track from adolescence into adulthood (Webber et al. 1991; Juhola et al. 2011), characterising the direction and magnitude of these changes is an important first step to identifying health trajectories that presage future disease risk.

Current literature on metabolic health during the adolescent transition has few notable shortcomings. First, a large proportion of the evidence base is composed of historical cohorts initiated prior to the obesity pandemic (Freedman et al. 1985; Webber et al. 1991; Blum et al. 1997; Mantzoros et al. 1997; Ahmed et al. 1999; Moran et al. 1999; Goran and Gower 2001; Eissa et al. 2016). Given that weight status affects not only metabolism (Coelho et al. 2013) but also timing of puberty (Lee et al. 2007; Lee et al. 2010), studies in contemporary populations are warranted to enhance relevance of research findings to present day youth. Second, most investigations were conducted in non-diverse populations – i.e., exclusively Caucasian (Tell et al. 1985; Bottner et al. 2004; Goharian et al. 2015) or with only two race/ethnic groups (Moran et al. 1999; Goran and Gower 2001; Bottner et al. 2004; Shankar et al. 2005; Eissa et al. 2016) – thereby limiting generalizability. Third, several of the studies had small sample sizes, with the majority of publications including fewer than 400 youth, and some with fewer than 100 participants) (Freedman et al. 1985; Mantzoros et al. 1997; Ahmed et al. 1999; Moran et al. 1999; Goran and Gower 2001; Bottner et al. 2004; Garces et al. 2010; Goharian et al. 2015; Tobisch et al. 2015). Metabolic aberrances may be difficult to detect early in the life course, and especially during adolescence given higher intra- and inter-individual variability in metabolism. Therefore, larger sample sizes will enhance statistical power to detect small but biologically relevant associations. Finally, no study to date has evaluated multiple biomarkers of cardiovascular and metabolic health (i.e., glycemia, adipokines, lipid profile, inflammation, and blood pressure). Given that chronic disease risk factors manifest in interrelated clusters rather than individually, assessing multiple aspects of metabolism will provide a more holistic picture of metabolic changes during puberty.

OBJECTIVES

In this study, we sought to: (1) characterise five-year changes in cardiovascular and metabolic risk biomarkers among 891 multi-ethnic youth aged 6–10 years at baseline; and (2) assess for differences in changes in biomarkers with respect to sex, baseline weight status, baseline pubertal status, and race/ethnicity.

SAMPLE & DATA COLLECTION

This study includes participants of Project Viva, an ongoing pre-birth cohort study recruited from a multi-specialty group practice in eastern Massachusetts (Atrius Harvard Vanguard Medical Associates). Details on study design and recruitment are reported elsewhere (Oken et al. 2015). Between 1999 and 2002, Project Viva enrolled 2128 pregnant women during their first trimester of pregnancy. Approximately seven years later, we carried out the mid-childhood research visit when children were 6–10 years of age (also referred to as “baseline” in this analysis) comprising anthropometric assessment, a fasting blood draw, and questionnaires. The mid-childhood visit was attended by 1116 of the original 2128 participants. Roughly five years after the mid-childhood visit, we conducted the early-teen visit (age 11–16 years; “follow-up”) which was attended by 1034 participants. The present analysis included 891 individuals for whom we had data on at least one of the metabolic biomarkers of interest at both time-points. The Institutional Review Board of Harvard Pilgrim Health Care approved all study protocols. All mothers provided written informed consent and children provided verbal assent.

Blood collection

At the mid-childhood (baseline) and early adolescence (follow-up) research visits, trained research assistants (RAs) collected an 8-hour fasting blood sample from the antecubital vein. All samples were refrigerated immediately, processed within 24 hours, and stored at −80°C until time of analysis.

Assessment of metabolic biomarkers

At both the mid-childhood and early adolescence visits, we used fasting blood to measure plasma glucose enzymatically, and to assay insulin using an electrochemiluminescence immunoassay (Roche Diagnostics, Indianapolis, IN). Using these values, we estimated insulin resistance using the homeostasis model assessment for insulin resistance [HOMA-IR= (glucose mg/dL × insulin $\mu IU/mL$)/405]. Serum total cholesterol, triglycerides, and high-density lipoprotein (HDL) were measured enzymatically with correction for endogenous glycerol. We calculated low-density lipoprotein (LDL) using the following equation: LDL = total cholesterol − HDL − (triglycerides/5). We measured plasma leptin and adiponectin concentrations via a radioimmunoassay (Linco Research, St Charles, MO). We used an immunoturbidimetric high-sensitivity assay on a Hitachi 911 analyzer to determine C-reactive protein (CRP) concentrations (Roche Diagnostics, Indianapolis, IN). Plasma interleukin-6 (IL-6) was measured by ultrasensitive enzyme-linked immunosorbent assay (ELISA).

At both research visits, we measured systolic blood pressure (SBP) using biannually-calibrated automated oscillometric monitors (Dinamap Pro100, Tampa, Florida). RAs recorded BP on the child's upper arm up to five times at one-minute intervals. We used the average of the five measurements for the statistical analysis and focused this analysis on SBP rather than diastolic blood pressure because it is directly and more reliably measured in children (Gillman and Cook 1995).

Weight and pubertal status

At the mid-childhood and early adolescence visits, RAs measured children's weight (kg) using an electronic scale (Tanita Corporation of America, Inc., Arlington Heights, IL) and height (cm) with a calibrated stadiometer (Shorr Productions, Olney, MD). We used these values to calculate body mass index (BMI, kg/m^2). We then standardised both BMI and height as percentiles and z-scores using the Centers for Disease Control (CDC) growth reference (Kuczmarski et al. 2002). We categorised participants as non-overweight/obese (BMI $<85^{th}$ percentile) and overweight/obese (BMI $\geq 85^{th}$ percentile) at the baseline (mid-childhood) visit.

At the mid-childhood research visit, mothers reported on pubarchal/pubertal phenotype based on appearance of body hair and breast development for girls; and body hair, facial hair, and deepening of voice for boys. For each characteristic, mothers selected from the following options: 1= "has not yet begun", 2 = "has barely started," 3 = "is definitely underway," or 4 = "seems complete." To create the baseline pubertal status variable, we combined the characteristics as an ordinal summary score of breast development and body hair for girls, and the mean of deepening of voice, facial hair, and body hair for boys. We then dichotomized the variable as pre-pubertal (puberty score=1) vs. pubertal (puberty score>1) as we have previously done (Perng et al. 2018). To explore potential differences in pubertal manifestations due to timing of adrenal vs. gonadal puberty, we also examined change in the metabolic biomarkers with respect to: (1) development of body hair for girls, and body hair and facial hair for boys as indicators of adrenal puberty; and (2) breast development as an indicator of gonadal puberty in girls only, as we do not have data on gonadal puberty in boys. To determine adrenal and gonadal pubertal status, we used the same approach of calculating an ordinal summary score and dichotomizing as puberty score=1 vs. puberty score>1.

Race/ethnicity

Using interviews, we collected information from the mothers about their child's race/ethnicity, which we subsequently classified as "White," "Black," "Hispanic," "Asian," "More than one race," and "Other." Given low sample sizes for the latter three categories, we combined them into "Other" for use in models when race/ethnicity was the predictor of interest. However, when we included race/ethnicity as a covariate, we used the original 6-category version.

Covariates

In addition to mutually adjusting child's sex, baseline weight status, baseline pubertal status, and race/ethnicity for each other, we also considered additional covariates for multivariable

and sensitivity analyses based *a priori* knowledge regarding determinants of metabolic health. These included: the child's age at baseline and follow-up, each calculated by subtracting the child's birth date (extracted from the medical record) from the date of the research visit; child's sex; and changes in the child's BMI and height z-scores as the difference between the early adolescence minus mid-childhood values.

DATA MANAGEMENT & STATISTICAL ANALYSIS

We calculated changes in each of the metabolic biomarkers by subtracting the mid-childhood biomarker value from his/her early adolescence value. At this time, we examined univariate distributions of these variables to assess for outliers, deviations from normality, and correlations among the biomarkers at baseline, follow-up, and change between baseline and follow-up.

Next, we examined associations of sex, baseline pubertal status, baseline weight status, and race/ethnicity with change in each biomarker using multivariable linear regression. In models where sex was the predictor of interest, Model 1 accounted for the child's age at baseline and follow-up, race/ethnicity, and baseline biomarker level. Model 2 further adjusted for baseline weight status and baseline pubertal status. For models where baseline weight status was the predictor, Model 1 accounted for child's sex, age at baseline and follow-up, and race/ethnicity, and Model 2 further adjusted for pubertal status. In models where pubertal status was the predictor, Model 1 was the same as for weight status, and Model 2 further accounted for baseline weight status. When we examined race/ethnicity as the predictor, we used a single model that accounted for child's sex, age at baseline and follow-up, baseline biomarker level, baseline weight status, and baseline pubertal status. Because change in adiposity can influence metabolic parameters, we examined whether the relationships changed after accounting for change in BMI z-score from mid-childhood to early adolescence as a proxy for adiposity accrual in children and adolescents (Inokuchi et al. 2011) in Model 3. In all models in which change in blood pressure was the outcome, we further adjusted for change in the child's height-for-age z-score, since height is a determinant of blood pressure (Regnault et al. 2014).

We assessed for effect modification by sex by testing for interactions with baseline pubertal status, weight status, and race/ethnicity. We considered evidence of effect modification where P-interaction ≤ 0.10.

All models met standard assumptions for multivariable linear regression (linearity of relationships between exposure/outcome pairs, homoscedasticity of model error, normality of residuals). All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Median age of the participants at the mid-childhood visit was 7.9 years (range: 6.6 to 10.9) and at the early adolescence visit was 13.1 years (range: 11.9, 16.6). Approximately half (50.2%) of the participants were male. Descriptive statistics for age, race/ethnicity, BMI z-score, waist circumference, weight status, and the metabolic biomarkers during mid-childhood (baseline) and in early adolescence (follow-up), as well as change between the

two time-points are presented in Table 1. During the five-year follow-up, fasting glucose and adiponectin decreased, while insulin HOMA-IR and leptin increased. Total and LDL decreased, but triglycerides increased. IL-6 increased, whereas no difference in CRP was detected. Blood pressure increased. Changes in most metrics were statistically significant during follow-up. Sex-specific values were similar to that of all children (Table S1). Correlations among metabolic biomarkers at baseline and follow-up, as well as among change in the biomarkers are shown in Table S2.

Table 2 shows associations of sex with the change in the metabolic biomarkers. After accounting for age at baseline and follow-up, baseline biomarker level, and race/ethnicity (Model 1), both sexes exhibited an increase in leptin during follow-up, but boys showed a smaller magnitude of increase than girls (−6.07 [95% CI: −8.38, −3.76] ng/mL). Conversely, adiponectin decreased, with boys showing a slightly larger decrement than girls (−0.66 [95% CI: −1.12, −0.20]). Blood pressure increased, with a larger increase in boys than girls (3.18 [95% CI: 2.11, 4.26] mmHg SBP). Adjusting for pubertal status and weight status at baseline did not change these results (Model 2).

Table 3 shows changes in the metabolic biomarkers with respect to baseline pubertal status. Leptin increased during follow-up for all participants, but children who had already started puberty experienced 8.37 (95% CI: 2.62, 14.11) ng/mL larger decrease in total cholesterol, and 6.96 (95% CI: 1.58, 3.83) ng/mL larger decrease in LDL than their pre-pubertal counterparts (Model 1). Accounting for baseline weight status in Model 2 did not materially change these estimates.

Table 4 shows relations of baseline overweight/obesity status with the metabolic biomarkers during follow-up. We observed increases in fasting insulin, HOMA-IR, and leptin, with a larger degree of increase in each biomarker among those who were overweight/obese at baseline (Model 1). Overweight/obese children also exhibited a larger decrement in adiponectin (−0.56 [95% CI: −1.10, −0.05] ng/mL) than their non-overweight/obese counterparts. CRP increased among overweight/obese youth (0.15 ± 0.36 mg/L), but decreased in nonoverweight/obese participants (0.15 ± 0.36 vs. −0.42 ± 0.33 mg/L). Adjustment for pubertal status (Model 2) did not change results.

In Table 5, we show associations of race ethnicity (White, Black, Hispanic, and other) with the metabolic biomarkers. Black youth showed steeper increases in insulin (6.70 [95% CI: 1.62, 11.79] μU/mL) and, to a lesser extent, HOMA-IR (1.98 [95% CI: 0.63, 3.32]) than Whites. Hispanic participants exhibited larger decreases in adiponectin (−1.82 [95% CI: −2.83, −0.81] ng/mL) and HDL (−4.96 [95% CI: −9.30, −0.62] mg/dL) than their White counterparts.

In Tables 2–5, adjustment for change in BMI z-score (Model 3 in Tables 2 and 3; Model 2 in Table 4) between mid-childhood and early adolescence did not materially change results. For example, when comparing change in leptin between boys vs. girls during follow-up, the estimate went from −5.76 (95% CI: −8.01, −3.50) ng/mL (Table 2, Model 2) to −5.76 (95% CI: −7.92, −3.60) ng/mL (Table 2, Model 3). Similarly, when comparing differences for change in insulin, HOMA-IR, and leptin between baseline overweight/obese vs. non-

overweight obese participants, the estimates were 5.64 (95% CI: 1.01, 10.28) μU/mL for insulin, 1.37 (95% CI: 0.19, 2.54) for HOMA-IR, and 9.96 (95% CI: 7.28, 12.64) ng/mL for leptin after adjusting for change in BMI z-score (Table 4, Model 3). Each of these estimates are similar in direction, magnitude, and precision to those reported in Table 4, Model 2. We also did not note any material change in results after accounting for change in the child's height-for-age z-score in models where change in SBP was the outcome (data not shown; available upon request).

In Table S3, we show estimates for associations of adrenal pubertal status with change in the biomarkers. Associations were similar to what we observed in Table 3, except the association with increasing leptin was statistically significant. We also evaluated associations with respect to breast development as a proxy for gonadal pubertal status in girls (Table S4). The estimates were similar to those for overall pubertal status shown in Table 3, except gonadal puberty in girls was not related to any of the lipids, but rather, was associated with a smaller increase in HOMA-IR.

When we tested for effect modification by sex for models where baseline pubertal status, baseline overweight/obesity status, and race/ethnicity were the explanatory variables of interest, we found non-significant interaction terms (P-interaction >>0.20) in all models except for the one testing the relationship between baseline pubertal status and leptin (P-interaction = 0.10). Thus, we further examined this association separately for boys and girls and noted diverging but non-significant associations across sexes. In the context of Model 1 (adjustment for age, baseline leptin, and race/ethnicity), boys showed 0.45 (95% CI: −3.05, 3.95) ng/mL decrease in leptin, whereas girls exhibited 3.75 (95% CI: −1.09, 8.60) ng/mL increase in leptin during follow-up. Accounting for baseline overweight/obesity (Model 2) attenuated these estimates to −0.73 (95% CI: −4.19, 2.74) ng/mL in boys, and 0.40 (95% CI: −4.25, 5.05) ng/mL in girls. Further adjustment for change in BMI z-score led to additional attenuation of estimates to −0.22 (95% CI: −3.64, 3.20) ng/mL in boys, and 0.18 (95% CI: −4.03, 4.38) ng/mL in girls.

COMMENTS

In this five-year prospective study of 891 U.S. youth aged 6–10 years at baseline, we characterised changes in multiple biomarkers of metabolic risk across early adolescence, and assessed for differences with respect to sex, baseline pubertal status, baseline weight status, and race/ethnicity.

Overall changes in metabolic biomarkers

During the follow-up period, we noted a marginal decrease in BMI z-score (an indicator of overall body size and adiposity (Freedman and Sherry 2009)), accompanied by increased waist circumference (a proxy for metabolically-active central visceral adiposity (Taylor et al. 2000)) and a 1.5% absolute increase in the proportion of overweight/obese participants. These changes in body composition were accompanied by changes in glycemia, including decreased fasting glucose, increased fasting insulin, and increased HOMA-IR. These associations likely reflect the rise in insulin secretion and reduction in insulin sensitivity during puberty (Caprio et al. 1989). We also noted increased leptin and decreased

adiponectin, which could be attributable to: (1) hormonal triggers of puberty initiation (i.e., the leptin surge (Clayton and Trueman 2000)); (2) the suppressive effect of rising gonadal hormones on adiponectin (Page et al. 2005; Tworoger et al. 2007); (3) changes in body composition that could impact adipocyte-derived cytokines, although it is not known whether changes in body composition precede changes in adipokines (Singh et al. 2016) or vice versa (Zhang et al. 2017).

In terms of lipid profile, our findings of a decrease total cholesterol and LDL over time align with those of adolescents in Project Heartbeat! (Eissa et al. 2016). The decrease may reflect usage of circulating cholesterols for production of sex steroid hormones that rise precipitously during puberty. On the other hand, in corroboration with previous findings in similarly-aged youth (Tell et al. 1985; Eissa et al. 2016), serum triglycerides increased during follow-up. This association may be related to the increase in HOMA-IR given the documented correlation between insulin resistance and hypertriglyceridemia (Glueck et al. 2009), although this relationship is not observed in persons of African descent (Yu et al. 2012).

Although we did not find any significant change in CRP, we noted a modest increase in IL-6. To our knowledge, there have not been any studies specifically examining changes to inflammatory biomarkers during puberty, the rise in IL-6 is not surprising given that it is a marker of low-grade inflammation, which is a widespread process that is likely upregulated during times of rapid growth and development.

Finally, in accordance with findings from Danish (Goharian et al. 2015) and Indian youth (Shankar et al. 2005), blood pressure increased across early adolescence. This increase could due to interactions of growth and gonadal hormones with pressor regulators (Helmer et al. 1952; Kienitz and Quinkler 2008), and/or could reflect peak somatic growth (Tu et al. 2009).

In addition to the overall changes in metabolic biomarkers during follow-up, we detected differences in the magnitude of change in several biomarkers with respect to sex, weight status, pubertal status, and race/ethnicity which are discussed below.

Differences by sex

We noted sex-specific differences in adipokine concentrations during follow-up. Specifically, girls exhibited a steeper increase in leptin than boys, but boys experienced a larger decrement in adiponectin. The difference in leptin change likely reflects the fact that leptin levels increase throughout adolescence in females (Apter 2003), but undergoes a temporary decrease at the initiation of puberty in males before stabilizing back to pre-pubertal levels (Mantzoros et al. 1997). The larger decrease in adiponectin in males was also observed in a study of 713 German children (Blum et al. 1997), and can be explained by the strong suppressive effect of testosterone on adiponectin (Page et al. 2005).

In addition to the biological explanations for sex-specific changes in adipokines, it is worth mentioning that these changes may have implications for metabolic health given that leptin and adiponectin regulate weight and metabolism through complementary actions (Cancello et al. 2004). Although high circulating leptin and low adiponectin are traditionally regarded

as consequences of excess fat mass, changes to adipokines can actually precede weight gain. For instance, in adults, high leptin in conjunction with overweight/obesity status suggests hypothalamic resistance to leptin's hunger-inhibiting effects (Mantzoros et al. 2011), which could lead to additional weight gain and further worsening of metabolic health over time. Similarly, increasing evidence in in youth and young adults indicates that altered leptin (both low and high) is a precursor to excess weight gain (Fleisch et al. 2007; Allard et al. 2013; Boeke et al. 2013).

We also detected a larger increase in SBP among boys than girls, which corroborates findings from an analysis of 86 boys and 66 girls in India that compared blood pressure three years before vs. three years after peak height growth velocity as a surrogate for puberty (Bottner et al. 2004). In this study, Shankfar et al. observed a 1.5 greater increase in SBP among males than females (~14.0 vs. ~8.6 mmHg in males vs. females) (Bottner et al. 2004). Accounting for change in BMI and height z-score did not change the results, suggesting that our finding reflects changes in blood pressure that are independent of growth. Possible mechanisms include increased secretion of hormones during puberty that interact with the renin-angiotensin system (Helmer et al. 1952; Gambling et al. 2004; Kienitz and Quinkler 2008) and a stronger impact of male than female hormones (Ely et al. 1997).

The size of increase in SBP (~3.2 mmHg) that we detected in boys is noteworthy given that elevated blood starting as early as childhood is an independent risk factor for future cardiovascular disease (Raitakari et al. 2003). In fact, among participants of the Bogalusa Heart Study, a difference in SBP of 1 mmHg during childhood predicted a cluster of metabolic risk factors in young adulthood (Rademacher et al. 2009).

Differences by baseline pubertal status

As compared to participants who were classified as pre-pubertal at baseline, those who had already started puberty experienced a more pronounced decrement in total and LDL cholesterol, which is likely because cholesterols are the primary substrates for production of sex steroid hormones that rise during puberty (Berg et al.). We observed similar associations with respect to adrenal pubertal status, which was based on presence of body and/or facial hair, but not with respect to gonadal puberty in girls, which was based on breast development.

The magnitude of effects we detected for changes in total (approximately 8 mg/dL decrease) and LDL (approximately 7 mg/dL decrease) with respect to baseline pubertal status are modest but may be relevant at the population level given that lipid profile during adolescence tracks across life and is a strong determinant of cardiovascular disease risk factors in adulthood (Li et al. 2003; Raitakari et al. 2003). However, it remains to be elucidated whether the decreases we observed in total and LDL cholesterol reflect a normal tracking of lipids across adolescence, or whether these are departures from healthy metabolic changes that have implications for long-term health.

Of note, we did not detect significant differences in leptin among pre- vs. post-pubertal participants. This is likely related to a "cancelling-out" of effects due to sex-specific leptin

trajectories (discussed in the above section): boys exhibit a temporary surge in leptin at the initiation of puberty followed by a decreased to pre-pubertal levels shortly thereafter (Mantzoros et al. 1997), while girls experience increased leptin across adolescence (Apter 2003). Assuming that the baseline assessment of leptin occurred around initiation of puberty for boys, our sex-stratified analysis reflect these biological phenomena: although all estimates were non-significant, we noted consistently negative beta estimates for the relationship between baseline pubertal status and change in leptin among boys, and consistently positive estimates in girls.

When we examined differences in biomarker with respect to gonadal pubertal status (based on breast development in girls), we observed a smaller magnitude of increase in HOMA-IR in pubertal vs. pre-pubertal females. This aligns with the spike in insulin resistance at the onset of puberty when breast development may not be readily apparent, followed by the return to pre-pubertal levels by the end of puberty (Moran et al. 1999).

Differences by baseline weight status

As compared to normal weight children, those who were overweight/obese at baseline exhibited a greater increase in biomarkers of glycemic regulation – namely, insulin, HOMA-IR, and leptin – despite a non-significant decrease in fasting glucose. The opposing direction of associations for change in insulin and HOMA-IR vs. change in fasting glucose likely mirrors the increase in insulin secretion during early puberty, which would temporarily result in lower circulating glucose levels.

Being overweight/obese also predicted adverse changes in adiponectin and HDL (larger decrease for both), and CRP (greater increase). Other studies have also reported more prominent changes in metabolism in obese than normal weight adolescents, with the most commonly studied metabolic parameter being insulin resistance and/or sensitivity (Roemmich et al. 2002; Brufani et al. 2009; Pilia et al. 2009). This phenomenon is likely due to the continued adverse influence of excess adiposity on metabolism.

Differences by race/ethnicity

When we explored differences in metabolic health by race/ethnicity, our main findings were that Blacks and Hispanics had worse metabolic biomarker changes than White participants. Specifically, Black adolescents experienced a sharper increase in insulin and HOMA-IR than Whites, and Hispanics exhibited a more pronounced decrement in adiponectin. These findings persisted after adjustment for change in BMI z-score and align with what is known of obesity-related ethnic health disparities that manifest in childhood, widen during adolescence, and persist into adulthood (Sheehan et al. 2003), and are likely due to a combination of lifestyle/environmental (Larson et al. 2015), psychosocial (Williams et al. 2016), and genetic factors (Qayyum et al. 2015).

Strengths & weaknesses

Strengths of this investigation include the multi-ethnic contemporary population, large sample size, ability to examine a suite of cardiovascular and metabolic biomarkers, and prospectively-collected research-grade data.

Weaknesses include the fact that we only had two repeated assessments of the biomarkers, which hampers our ability to capture more nuanced fluctuation in metabolic health during early adolescence; mother-reported (rather than physician-evaluation) assessment of child pubertal status, which is vulnerable reporting error; low sample sizes for Asian and mixed race participants; and the fact that Project Viva participants all had health insurance and are relatively well-educated, which may limit generalizability of our findings to lower socioeconomic settings. Finally, we cannot discount the possibility of chance findings given the large number of models tested. However, our research focus was to describe and assess the direction, magnitude, and precision of the estimates rather than focus on statistical significance, especially in light of the fact that many of the biomarkers are correlated measures of the same biological concept (e.g. fasting insulin, fasting glucose, HOMA-IR, leptin, and adiponectin are all measures of glycemia).

CONCLUSIONS

In this study, we characterised change in glycemia, adipokines, lipid profile, inflammation, and blood pressure across early adolescence, and identified differences in patterns by sex, baseline weight status, baseline pubertal status, and race/ethnicity. Several biomarkers worsened over follow-up (e.g., increased fasting insulin and insulin resistance, increased leptin and decreased adiponectin, increased inflammation, increased blood pressure), and we generally noted less favorable changes in boys than girls, among participants who were overweight/obese at baseline, and in Black and Hispanic participants. Given that puberty is transitional life stage characterized by rapid physiological changes, future studies are required to investigate the extent to which these changes correlate with health outcomes beyond adolescence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Descriptive statistics for metabolic biomarkers during mid-childhood (baseline) and the early teens (follow-up) in 891 Project Viva participants.

	Mean ± SD or % (N)			*P*-value[a]
	Baseline	**Follow-up**	**Change**	
Child characteristics				
Age (years)	7.9 ± 0.8	13.1 ± 0.9	5.2 ± 0.9	<0.0001
% Male	50.2% (447)	--	--	--
Race/ethnicity, % (N)				
White	64.7% (576)	--	--	--
Black	16.1% (143)	--	--	--
Hispanic	4.5% (40)	--	--	--
Other	14.7% (131)	--	--	--
BMI z-score	0.40 ± 1.00	0.37 ± 1.06	−0.04 ± 0.61	0.06
Waist circumference (cm)	59.9 ± 8.2	72.8 ± 11.6	12.8 ± 7.7	<0.0001
Overweight/obese, % (N)	25.4% (225)	26.9% (239)	1.5%	<0.0001
Pubertal, % (N)	21.6% (187)	89.3% (792)	67.7%	<0.0001
Metabolic biomarkers				
Glucose (mg/dL)	95.5 ± 15.4	92.2 ± 15.7	−3.5 ± 20.7	0.002
Insulin (μU/mL)	8.0 ± 6.6	16.3 ± 18.3	8.8 ± 18.6	<0.0001
HOMA−IR	1.9± 1.9	3.3 ± 3.8	1.7 ± 4.4	<0.0001
Leptin (ng/mL)	6.0 ± 7.3	11.8 ± 13.9	6.0 ± 12.0	<0.0001
Adiponectin (ng/mL)	15.2 ± 8.5	6.4 ± 2.8	−9.2 ± 7.7	<0.0001
Total cholesterol (mg/dL)	160.1 ± 27.4	156.1 ± 28.0	−5.1 ± 26.3	<0.0001
HDL (mg/dL)	57.0 ± 23.5	55.7 ± 13.4	−0.9 ± 12.1	0.12
LDL (mg/dL)	91.6 ± 22.9	86.5 ± 23.9	−6.1 ± 20.4	<0.0001
Triglycerides (mg/dL)	57.6 ± 23.5	69.4 ± 30.6	9.9 ± 29.6	<0.0001
CRP (mg/L)	1.0 ± 3.0	0.9 ± 1.9	−0.1 ± 3.0	0.43
IL−6 (pg/mL)	1.0 ± 1.4	1.3 ± 2.7	0.3 ± 3.2	0.02
SBP (mmHg)	94.7 ± 8.6	107.1 ± 9.1	12.5 ± 9.9	<0.0001

HOMA-IR: homeostatic model insulin resistance; **HDL:** high-density lipoprotein; **LDL:** low-density lipoprotien; **CRP:** C-reactive protein; **IL-6**: interleukin-6; **SBP:** systolic blood pressure

[a]From a paired sample t-test for continuous variables; from a Pearson Chi-squared test for % overweight/obese and % pubertal.

Table 2

Adjusted estimates for change in each biomarker during follow-up with respect to sex among Project Viva participants.

	Model 1			Model 2	Model 3
	Mean ± SE		β (95% CI)[a]	β (95% CI)[a]	β (95% CI)[a]
	Boys	Girls	Boys vs. girls	Boys vs. girls	Boys vs. girls
N	*n=447*	*n=443*			
ΔGlucose (mg/dL)	−3.96 ± 3.23	−6.44 ± 3.35	2.47 (−1.06, 6.01)	2.36 (−1.32, 6.04)	2.47 (−1.22, 6.16)
ΔInsulin (μU/mL)	9.18 ± 3.44	8.02 ± 3.58	1.16 (−2.42, 4.84)	0.59 (−3.16, 4.34)	0.68 (−3.07, 4.43)
ΔHOMA−IR	1.80 ± 0.83	1.73 ± 0.87	0.07 (−0.87, 1.00)	−0.05 (−1.00,0.90)	−0.04 (−0.99, 0.91)
ΔLeptin (ng/mL)	3.23 ± 2.17	9.30 ± 2.22	**−6.07 (−8.38, −3.76)**	**−5.76 (−8.01, −3.50)**	**−5.76 (−7.92, −3.60)**
ΔAdiponectin (ng/mL)	−10.03 ± 0.44	−9.37 ± 0.45	**−0.66 (−1.12, −0.20)**	**−0.66 (−1.14, −0.18)**	**−0.67 (−1.14, −0.21)**
ΔTotal cholesterol (mg/dL)	−2.61 ± 4.24	−0.83 ± 4.37	−1.78 (−6.12, 2.56)	−2.58 (−7.05, 1.89)	−2.42 (−6.89, 2.05)
ΔHDL (mg/dL)	−2.08 ± 2.00	−0.69 ± 2.05	−1.38 (−3.44, 0.68)	−1.47 (−3.55, 0.61)	−1.70 −3.69, 0.29)
ΔLDL (mg/dL)	−3.60 ± 3.38	−2.92 ± 3.50	−0.68 (−4.16, 2.80)	−1.17 (−4.76, 2.42)	−0.81 (−4.33,2.70)
ΔTriglycerides (mg/dL)	10.72 ± 5.09	9.76 ± 5.25	0.96 (−4.29, 6.21)	0.78 (−4.63, 6.19)	1.21 (−4.12,6.54)
ΔCRP (mg/L)	−0.24 ± 0.33	−0.30 ± 0.34	0.05 (−0.30, 0.40)	0.07 (−0.30, 0.43)	0.05 (−0.31, 0.41)
ΔIL−6 (pg/mL)	0.23 ± 0.57	0.61 ± 0.58	−0.37 (−0.97, 0.22)	−0.42 (−1.04, 0.21)	−0.42 (−1.05, 0.20)
ΔSBP (mmHg)	13.7 ± 1.1	10.5 ± 1.1	**3.18 (2.11, 4.26)**	**3.20 (2.10, 4.30)**	**3.17 (2.08, 4.27)**

HOMA-IR: homeostatic model insulin resistance; **HDL:** high-density lipoprotein; **LDL:** low-density lipoprotein; **CRP:** C-reactive protein; **IL-6:** interleukin-6; **SBP:** systolic blood pressure

[a]Bolded font indicates statistical significance at $P<0.05$.

Model 1 Adjusted for age at baseline and follow-up, baseline biomarker level,and race/ethnicity.

Model 2 Model 1 + pubertal status (pre-pubertal vs. pubertal) and weight status (non-overweight/obese vs. overweight/obese) at baseline

Model 3 Model 2 + change in BMI z-score

Table 3

Adjusted estimates for change in each biomarker during follow-up with respect to pubertal status at baseline among Project Viva participants.

	Model 1			Model 2	Model 3
	Mean ± SE		β (95% CI)[a]	β (95% CI)[a]	β (95% CI)[a]
	Pre-pubertal	Pubertal	Pubertal vs. pre-pubertal	Pubertal vs. pre-pubertal	Pubertal vs. pre-pubertal
	n = 677	*n = 187*			
ΔGlucose (mg/dL)	−5.01 ± 3.23	−6.48 ± 3.71	−1.48 (−6.15, 3.19)	−2.0 (−6.76, 2.74)	−1.99 (−6.76, 2.79)
ΔInsulin (μU/mL)	9.14 ± 3.43	6.77 ± 3.91	−2.37 (−7.21, 2.47)	−3.13 (−8.00, 1.74)	−2.82 (−7.70, 2.05)
ΔHOMA−IR	1.78 ± 0.82	1.55 ± 0.95	−0.23 (−1.47, 1.01)	−0.45 (−1.70, 0.79)	−0.40 (−1.65, 0.85)
ΔLeptin (ng/mL)	5.65 ± 2.13	7.28 ± 2.42	1.62 (−1.44, 4.68)	0.31 (−2.65,3.27)	0.68 (−2.15, 3.52)
ΔAdiponectin (ng/mL)	−9.69 ± 0.44	−9.62 ± 0.50	0.07 (−0.55, 0.69)	0.22 (−0.41, 0.84)	0.16 (−0.45, 0.77)
ΔTotal cholesterol (mg/dL)	0.26 ± 4.20	−8.11 ± 4.74	**−8.37 (−14.11, −2.62)**	**−7.99 (−13.86, −2.13)**	**−7.68 (−13.55, −1.81)**
ΔHDL (mg/dL)	−1.06 ± 1.97	−2.18 ± 2.22	−1.13 (−3.83, 1.58)	−0.31 (−3.02,2.40)	−0.86 (−3.47, 1.74)
ΔLDL (mg/dL)	−1.61 ± 3.36	−8.57 ± 3.80	**−6.96 (−11.57, −2.34)**	**−7.15 (−11.85, −2.44)**	**−6.45 (−11.05, −1.84)**
ΔTriglycerides (mg/dL)	10.57 ± 5.07	8.68 ± 5.72	−1.89 (−8.86, 5.09)	−3.33 (−10.41, 3.76)	2.41 (−9.39, 4.58)
ΔCRP (mg/L)	−0.17 ± 0.34	−0.48 ± 0.38	−0.32 (−0.78, 0.15)	−0.46 (−0.93, 0.02)	−0.43 (−0.90, 0.04)
ΔIL−6 (pg/mL)	0.54 ± 0.57	0.05 ± 0.65	−0.49 (−1.30, 0.31)	−0.67 (−1.49, 0.16)	−0.66 (−1.48, 0.16)
ΔSBP (mmHg)	11.90± 1.07	12.48± 1.16	0.57 (−0.86, 2.01)	0.47 (−0.98, 1.92)	0.59 (−0.85, 2.03)

HOMA-IR: homeostatic model insulin resistance; **HDL:** high-density lipoprotein; **LDL:** low-density lipoprotein; **CRP:** C-reactive protein; **IL-6:** interleukin-6; **SBP:** systolic blood pressure

[a]Bolded font indicates statistical significance at $P<0.05$.

Model 1 Adjusted for sex, age at baseline and follow-up, baseline biomarker level, and race/ethnicity.

Model 2 Model 1 + weight status at baseline (overweight/obese vs. non-overweight/obese).

Model 3 Model 2 + change in BMI z-score

Table 4

Adjusted estimates for change in each biomarker during follow-up with respect to baseline overweight/obese (OW/OB) status at baseline among Project Viva participants.

	Model 1			Model 2	Model 3
	Mean ± SE		β (95% CI)[a]	β (95% CI)[a]	β (95% CI)[a]
	Non−OW/OB	OW/OB	OW/OB vs. non-OW/OB	OW/OB vs. non-OW/OB	OW/OB vs. non-OW/OB
All children	***n = 660***	***n=225***			
ΔGlucose (mg/dL)	−5.94 ± 3.21	−3.29 ± 3.52	2.65 (−1.38,6.68)	2.54 (−1.66, 6.74)	2.57 (−1.74, 6.88)
ΔInsulin (μU/mL)	7.58 ± 3.41	12.37 ± 3.83	**4.79 (0.34, 9.26)**	**4.88 (0.32, 9.43)**	**5.64 (1.01,10.28)**
ΔHOMA−IR	1.45 ± 0.82	2.76 ± 0.92	**1.30 (0.18, 2.43)**	**1.25 (0.10, 2.40)**	**1.37 (0.19, 2.54)**
ΔLeptin (ng/mL)	3.87 ± 2.03	12.46 ± 2.23	**8.59(5.95,11.24)**	**8.39 (5.65,11.14)**	**9.96 (7.28,12.64)**
ΔAdiponectin (ng/mL)	−9.52 ± 0.43	−10.09 ± 0.47	**−0.57 (−1.10, −0.05)**	**−0.63 (−1.18, −0.08)**	**−0.87 (−1.41, −0.34)**
ΔTotal cholesterol (mg/dL)	−1.20 ± 4.22	−3.39 ± 4.59	−2.20 (−7.14, 2.75)	−1.66 (−6.76, 3.45)	−0.84 (−6.05, 4.37)
ΔHDL (mg/dL)	−0.31 ± 1.96	−3.87 ± 2.11	**−3.57 (−5.90, −1.23)**	**−3.80 (−6.20, −1.41)**	**−4.26 (−7.60, −2.92)**
ΔLDL (mg/dL)	−3.33 ± 3.36	−3.18 ± 3.68	0.15 (−3.83, 4.13)	0.78 (−3.33, 4.89)	2.60 (−1.50, 6.69)
ΔTriglycerides (mg/dL)	8.62 ± 5.05	14.62 ± 5.48	6.00 (−0.04, 12.04)	**6.46 (0.20,12.72)**	**8.76 (2.47,15.04)**
ΔCRP (mg/L)	−0.42 ± 0.33	0.15 ± 0.36	**0.57 (0.16, 0.97)**	**0.65 (0.23,1.06)**	**0.74 (0.32,1.17)**
ΔIL−6 (pg/mL)	0.26 ± 0.56	0.85 ± 0.61	0.59 (−0.10, 1.27)	**0.71 (0.00,1.43)**	**0.73 (0.00,1.47)**
ΔSBP (mmHg)	11.95 ± 1.06	12.83 ± 1.17	0.88 (−0.43, 2.18)	0.57 (−0.77, 1.91)	1.02 (−0.33, 2.37)

HOMA-IR: homeostatic model insulin resistance; **HDL**: high-density lipoprotein; **LDL**: low-density lipoprotein; **CRP**: C-reactive protein;**IL-6**: interleukin-6; **SBP**: systolic blood pressure

[a]Bolded font indicates statistical significance at $P<0.05$.

Model 1 Adjusted for sex, age at baseline and follow-up, baseline biomarker level, and race/ethnicity.

Model 2 Model 1 + pubertal status (pre-pubertal vs. pubertal) at baseline

Model 3 Model 2 + change in BMI z-score

Table 5

Adjusted estimates for change in metabolic biomarkers during follow-up with respect to race/ethnicity among Project Viva participants.

	Mean ± SE				β (95% CI)		
	Model 1						
	White *n = 564*	**Black** *n = 134*	**Hispanic** *n=38*	**Other** *n = 125*	**Black vs. White**	**Hispanic vs. White**	**Other vs. White**
ΔGlucose (mg/dL)	−3.46 ± 1.19	−2.60 ± 2.33	−3.81 ± 3.99	−4.62 ± 2.47	0.86 (−4.30, 6.02)	−0.35 (−6.43, 7.71)	−1.16 (−6.43, 4.12)
ΔInsulin (uU/mL)	7.70 ± 1.22	14.40 ± 2.26	7.03 ± 3.83	6.20 ± 2.54	**6.70 (1.62, 11.79)**	−0.68 (−8.51, 7.16)	−1.50 (−6.94, 3.94)
ΔHOMA−IR	1.28 ± 0.31	3.26 ± 0.61	1.26 ± 1.00	1.22 ± 0.63	**1.98 (0.63, 3.32)**	−0.01 (−2.05, 2.02)	−0.06 (−1.41, 1.29)
ΔLeptin (ng/mL)	5.09 ± 0.73	7.92 ± 1.35	7.25 ± 2.28	5.92 ± 1.56	2.83 (−0.19, 5.85)	2.17 (−2.50, 6.84)	0.84 (−2.48, 4.16)
ΔAdiponectin (ng/mL)	−8.97 ± 0.16	−9.35 ± 0.29	−10.79 ± 0.49	−9.19 ± 0.33	−0.39 (−1.04, 0.26)	**−1.82 (−2.83, −0.81)**	−0.23 (−0.94, 0.49)
ΔTotal cholesterol (mg/dL)	−4.85 ± 1.46	0.02 ± 2.76	−12.12 ± 4.60	−7.25 ± 3.16	4.87 (−1.32, 11.06)	−7.27 (−16.70, 2.16)	−2.40 (−9.12, 4.33)
ΔHDL (mg/dL)	−0.60 ± 0.68	0.78 ± 1.28	−5.56 ± 2.12	−1.56 ± 1.45	1.38 (−1.49, 4.25)	**−4.96 (−9.30, −0.62)**	−0.96 (−4.06, 2.14)
ΔLDL (mg/dL)	−6.46 ± 1.17	−1.71 ± 2.22	−9.10 ± 3.69	−7.37 ± 2.53	4.75 (−0.22, 9.72)	−2.63 (−10.19, 4.93)	−0.91 (−6.29, 4.47)
ΔTriglycerides (mg/dL)	11.16 ± 1.76	4.86 ± 3.34	12.21 ± 5.54	7.69 ± 3.80	−6.29 (−13.80, 1.20)	1.05 (−10.30, 12.39)	−3.48 (−11.55,4.60)
ΔCRP (mg/L)	−0.04 ± 0.12	−0.16 ± 0.22	0.23 ± 0.36	−0.37 ± 0.25	−0.12 (−0.62, 0.38)	0.27 (−0.47, 1.01)	−0.33 (−0.87, 0.21)
ΔIL−6 (pg/mL)	0.45 ± 0.20	0.25 ± 0.38	0.94 ± 0.64	0.01 ± 0.44	−0.20 (−1.05, 0.65)	0.49 (−0.81, 1.80)	−0.44 (−1.37, 0.49)
ΔSBP (mmHg)	12.27 ± 0.35	12.95 ± 0.73	14.42 ± 1.36	12.29 ± 0.73	0.68 (−0.92, 2.28)	2.15 (−0.60, 5.91)	0.03 (−1.56, 1.61)
	Model 2						
	White *n = 562*	**Black** *n = 134*	**Hispanic** *n= 38*	**Other** *n = 125*	**Black vs. White**	**Hispanic vs. White**	**Other vs. White**
ΔGlucose (mg/dL)	−3.38 ± 1.20	−2.65 ± 2.34	−3.86 ± 3.99	−4.65 ± 2.47	0.73 (−4.45, 5.92)	−0.47 (−8.55, 7.60)	−1.26 (−6.54, 4.01)
ΔInsulin (μU/mL)	7.83 ± 1.22	14.18± 2.26	6.76 ± 3.83	6.17± 2.54	**6.35 (1.26, 11.43)**	−1.07 (−8.91, 6.76)	−1.66 (−7.09, 3.77)
ΔHOMA−IR	1.30 ± 0.31	3.21 ± 0.61	1.23 ± 1.01	1.22 ± 0.63	**1.91 (0.56, 3.26)**	−0.07 (−2.10, 1.97)	−0.08 (−1.43, 1.27)
ΔLeptin (ng/mL)	5.27 ± 0.70	7.66 ± 1.29	6.67 ± 2.19	5.79 ± 1.50	2.39 (−0.51, 5.29)	1.40 (−3.08, 5.88)	0.52 (−2.66, 3.70)
ΔAdiponectin (ng/mL)	−8.97 ± 0.15	−9.25 ± 0.28	−10.67 ± 0.48	−9.13 ± 0.32	−0.28 (−0.91, 0.35)	**−1.70 (−2.68, −0.73)**	−0.16 (−0.85, 0.53)
ΔTotal cholesterol (mg/dL)	−4.70 ± 1.47	−0.22 ± 2.76	−12.38 ± 4.60	−7.33 ± 3.16	4.48 (−1.72, 10.68)	−7.68 (−17.10, 1.75)	−2.63 (−9.35, 4.09)
ΔHDL (mg/dL)	−0.80 ± 0.65	1.23 ± 1.23	−5.09 ± 2.03	−1.44 ± 1.39	2.03 (−0.73, 4.78)	**−4.29 (−8.45, −0.13)**	−0.64 (−3.61, 2.33)
ΔLDL (mg/dL)	−6.18 ± 1.15	−2.24 ± 2.17	−9.75 ± 3.61	−7.55 ± 2.48	3.94 (−0.92, 8.81)	−3.57 (−10.97, 3.82)	−1.37 (−6.63, 3.89)

	Model 2						
	White ***n = 562***	**Black** ***n = 134***	**Hispanic** ***n= 38***	**Other** ***n = 125***	**Black vs. White**	**Hispanic vs. White**	**Other vs. White**
ΔTriglycerides (mg/dL)	11.57 ± 1.75	4.24 ± 3.30	11.47 ± 5.47	7.54 ± 3.74	−7.33 (−14.73, 0.07)	−0.10 (−11.28, 11.08)	−4.03 (−11.98,3.93)
ΔCRP (mg/L)	−0.03 ± 0.12	−0.16 ± 0.22	0.19± 0.36	−0.39 ± 0.25	−0.12 (−0.62, 0.37)	0.22 (−0.52, 0.96)	−0.36 (−0.90, 0.18)
ΔIL−6 (pg/mL)	0.44 ± 0.21	0.25 ± 0.38	0.93 ± 0.64	0.00 ± 0.44	−0.20 (−1.05, 0.66)	0.49 (−0.82, 1.80)	−0.44 (−1.37, 0.49)
ΔSBP (mmHg)	12.28 ± 0.35	12.80 ± 0.73	14.37 ± 1.35	12.22 ± 0.73	0.52 (−1.07, 2.11)	2.09 (−0.64, 4.83)	−0.05 (−1.62, 1.52)

HOMA-IR: homeostatic model insulin resistance; **HDL**: high-density lipoprotein; **LDL**: low-density lipoprotein; **CRP**: C-reactive protein; **IL-6**: interleukin-6; **SBP**: systolic blood pressure

Model 1: Adjusted for sex, age at baseline and follow-up, and baseline biomarker level, weight status, and pubertal status. Bolded font indicates statistical significance at $P<0.05$.

Model 2: Model 1 + change in BMI z-score