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Salivary Epigenetic Measures of Body Mass Index and Social Determinants of Health Across Childhood and Adolescence

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IMPORTANCE Children who are socioeconomically disadvantaged are at increased risk for high body mass index (BMI) and multiple diseases in adulthood. The developmental origins of health and disease hypothesis proposes that early life conditions affect later-life health in a manner that is only partially modifiable by later-life experiences.

OBJECTIVE To examine whether epigenetic measures of BMI developed in adults are valid biomarkers of childhood BMI and if they are sensitive to early life social determinants of health.

DESIGN, SETTING, AND PARTICIPANTS This population-based study of over 3200 children and adolescents aged 8 to 18 years included data from 2 demographically diverse US pediatric cohort studies that combine longitudinal and twin study designs. Analyses were conducted from 2021 to 2022.

EXPOSURES Socioeconomic status, marginalized groups.

MAIN OUTCOME AND MEASURE Salivary epigenetic BMI, BMI. Analyses were conducted to validate the use of saliva epigenetic BMI as a potential biomarker of child BMI and to examine associations between epigenetic BMI and social determinants of health.

RESULTS Salivary epigenetic BMI was calculated from 2 cohorts: (1) 1183 individuals aged 8 to 18 years (609 female [51%]; mean age, 13.4 years) from the Texas Twin Project and (2) 2020 children (1011 female [50%]) measured at 9 years of age and 15 years of age from the Future of Families and Child Well-Being Study. Salivary epigenetic BMI was associated with children's BMI ($r = 0.36$; 95% CI, 0.31-0.40 to $r = 0.50$; 95% CI, 0.42-0.59). Longitudinal analysis found that epigenetic BMI was highly stable across adolescence but remained both a leading and lagging indicator of BMI change. Twin analyses showed that epigenetic BMI captured differences in BMI between monozygotic twins. Moreover, children from more disadvantaged socioeconomic status ($b = -0.13$ to -0.15 across samples) and marginalized racial and ethnic groups ($b = 0.08$-0.34 across samples) had higher epigenetic BMI, even when controlling for concurrent BMI, pubertal development, and tobacco exposure. Socioeconomic status at birth relative to concurrent socioeconomic status best predicted epigenetic BMI in childhood and adolescence ($b = -0.15$; 95% CI, -0.20 to -0.09).

CONCLUSION AND RELEVANCE This study demonstrated that epigenetic measures of BMI calculated from pediatric saliva samples were valid biomarkers of childhood BMI and may be associated with early-life social inequalities. The findings are in line with the hypothesis that early-life conditions are especially important factors in epigenetic regulation of later-life health. Research showing that health later in life is linked to early-life conditions has important implications for the development of early-life interventions that could significantly extend healthy life span.

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Children who are socioeconomically disadvantaged are at increased risk for high body mass index (BMI) and multiple diseases in adulthood.[1] The developmental origins of health and disease hypothesis proposes that early-life conditions affect later-life health in a manner that is only partially modifiable by later-life experiences.[2,3] Epigenetic mechanisms, including DNA methylation (DNAm), are thought to be involved in the biological embedding of early-life conditions that affect aging-related health.[4,5] Next-generation DNAm measures of biological aging that were developed to predict multi-system physiological decline, health behaviors, and/or mortality are promising new tools to study social determinants of health.[6] A closely related set of studies has developed composite epigenetic measures of BMI based on analysis of adult blood samples (epigenetic BMI).[7-9] Similar to measures of biological aging, epigenetic BMI has been found to be associated with health and mortality in adults, including levels of triglycerides, hemoglobin A1$_c$, high-density lipoprotein cholesterol, type 2 diabetes, and cardiovascular disease, beyond phenotypic BMI and chronological age.[7,8] Whether these epigenetic BMI measures can be applied in children, however, is unclear.

The exposures and biological processes that affect epigenetic BMI are likely similar to those affecting epigenetic measures of biological aging, because metabolic processes appear to be causally involved in biological aging and next-generation epigenetic measures of biological aging were developed to predict BMI, among other measures.[10,11] Studies in pediatric saliva samples suggest that epigenetic profiles of biological aging developed in adults are sensitive to social determinants of health experienced in real-time during childhood and adolescence.[12-14] These results are encouraging for researchers interested in epigenetics in childhood, because, compared with blood collections, saliva samples are especially amenable to pediatric and hard-to-reach samples.

However, there remains considerable uncertainty about the validity of applying epigenetic measures that were developed in adult blood samples to children's saliva samples for 3 reasons. First, DNAm is a primary mechanism of cell differentiation and is, therefore, tissue specific.[15] Second, tissue composition across the body varies with age and sex, which could confound comparisons across the life span.[16] Third, genomic research has overwhelmingly relied on analysis of blood samples from adults of European ancestry, potentially limiting the portability of DNAm measures to diverse samples of children, for whom saliva is the most common and feasible biofluid to collect. Examining associations of saliva epigenetic BMI with child BMI, therefore, presents a unique opportunity to validate the usage of blood-based DNAm measures developed to predict adult health in pediatric saliva samples.

Here, we examine (1) whether epigenetic BMI previously developed in adult blood samples is a valid biomarker of children's BMI, when measured in saliva DNAm and (2) whether child epigenetic BMI is sensitive to social determinants of health, as indexed by socioeconomic status and marginalized racial and ethnic identities in childhood and adolescence. To accomplish these goals, we analyzed data from 2 demographically diverse pediatric cohorts that combine longitudinal and twin study designs. Our research builds on a previous blood-based epigenome-wide study[9] that identified 278 DNAm sites associated with BMI in 5387 adults of European and/or Indian Asian ancestry.[9] We used these results to compute salivary epigenetic BMI in 1183 individuals aged 8 to 18 years from the Texas Twin Project (TTP) and in 2020 children measured at 9 years of age and again at 15 years of age in the Future of Families and Child Well-Being Study (FFCW).

Key Points

Question Can the long arm of childhood on aging-related health be measured in real time?

Findings In this study that analyzed data from 2 US cohort studies, epigenetic measures of body mass index developed in adults were valid biomarkers of children's body mass index and were associated with socioeconomic and racialized inequalities experienced in childhood, especially at birth.

Meaning These findings are in line with the hypothesis that early-life conditions are especially important factors in epigenetic regulation of later-life health.

Methods

Sample

The TTP[17] is an ongoing longitudinal study that includes the collection of saliva samples for DNA and DNAm extraction. Participants in the current study were 1213 children and adolescents (622 female [51%]), including 433 monozygotic and 780 dizygotic twins from 617 unique families, aged 8 to 19 years (mean [SD] age, 13.66 [3.06] years), who had at least 1 DNAm sample. A total of 195 participants contributed 2 DNAm samples (time between repeated samples; mean [SD], 22 [6.5] months; range, 3 to 38 months) and 16 samples were assayed in duplicate for reliability analyses (total methylation sample, 1424). Participants self-identified race and ethnicity defined by study protocol as African American/Black and potentially another race and ethnicity (120 [10%]), Asian and potentially another race and ethnicity but not Latinx or Black (90 [7.5%]), Hispanic/Latinx only (147 [12%]), Hispanic/Latinx and White (97 [8%]), Indigenous American, Pacific Islander, or other (participants could select that they were another race or ethnicity but they did not have to specify which), but not Hispanic/Latinx, Black, or Asian (7 [0.6%]), and White only (752 [62%]). The University of Texas institutional review board granted ethical approval.

The FFCW study follows a sample of 4898 children born in large US cities from 1998 through 2000. The FFCW oversampled children born to unmarried parents and interviewed parents at birth and ages 1, 3, 5, 9, and 15 years. During home visits, BMI was measured and saliva DNA was collected at ages 9 and 15 years (N = 3100). Saliva DNAm data were assayed on a two-thirds sample (n = 2020) using the Illumina 450K and EPIC methylation arrays with ages 9 and 15 years assayed on the same plate. DNAm study participants self-identified race and ethnicity defined by study protocol as African American/

Black only (1009 [50%]), Asian or other (52 [2%]), Hispanic/Latinx (444 [22%]), multiracial (116 [5%]), and White (399 [20%]). The University of Michigan and Princeton University institutional review boards granted ethical approval. Informed written consent was obtained from study participants' legal guardians in both cohorts. We used Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines. See the **Table** for description of study measures, eMethods in Supplement 2 for preprocessing of DNA and DNAm, and eTable 1 in Supplement 1 for descriptive statistics.

Statistical Analyses

We conducted 6 sets of analyses. Analyses 1 through 3 validated the use of saliva epigenetic BMI as a biomarker of child BMI in (1) cross-sectional regression models, (2) longitudinal analyses, and (3) in a bivariate biometric model (ie, the ACE statistical model). The first longitudinal analysis was a fixed-effects regression model to examine the correlation of within-person changes in BMI with changes in epigenetic BMI, adjusting for unobserved time-invariant variables.[25] With 2 observations per person, this model reduces to an OLS regression using observed difference scores for the time-varying outcome variable. The second longitudinal analysis was a bivariate random intercept cross-lagged panel model to test whether epigenetic BMI at age 9 years can incrementally improve estimating future BMI, beyond BMI at age 9 years and time-invariant factors, such as stable genetic effects and time-invariant factors, such as stable genetic effects.[26] The ACE statistical model used the covariation between monozygotic twins and dizygotic twins to decompose the association between epigenetic BMI and BMI into components representing additive genetic factors (component A), environmental factors shared by twins living in the same home (component C), and environmental factors unique to each twin and stochastic variation (component E).[27] Monozygotic (ie, identical) twins are nearly identical for their DNA sequence, so if differences in epigenetic BMI between twins are associated with differences between them in their BMI, this association is unlikely to be attributable to genes that influence both phenotypes.[28]

Analyses 4 through 6 examined associations between epigenetic BMI and social determinants of health in (4) cross-sectional regression models of socioeconomic status and epigenetic BMI, (5) cross-sectional regression models of epigenetic BMI and racial and ethnic groups, and (6) longitudinal models examining socioeconomic status and epigenetic BMI using both a fixed-effect regression model and a random intercept cross-lagged panel model. Analyses 5 and 6 tested if children growing up in more socioeconomically disadvantaged circumstances and children from marginalized racial and ethnic groups showed higher concurrent epigenetic BMI and whether these associations were robust controlling for concurrent BMI, pubertal development, and tobacco exposure. The longitudinal models for analysis 6 examined how changes in SES from ages 9 to 15 years, as well as SES measured at birth, were associated with changes in epigenetic BMI from ages 9 to 15 years.

Prior to all analyses, epigenetic BMI measures were residualized for technical artifacts, including array (Illumina Epic
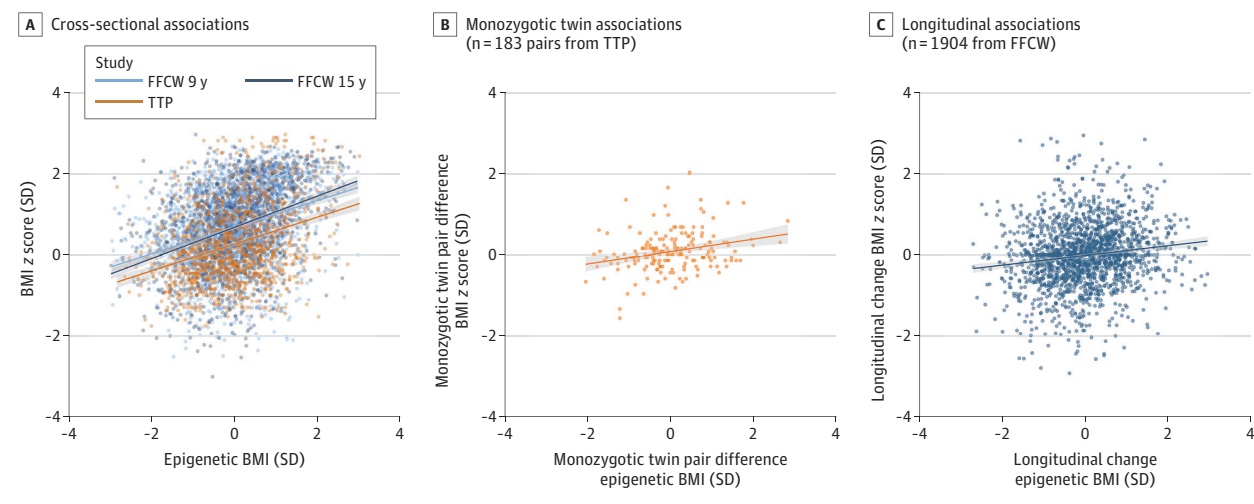
or 450k chips), slide, batch, and estimated salivary cell composition. All models included age, sex, and an age-by-sex interaction as covariates of epigenetic BMI. No statistical correction for multiple comparisons was made. R version 4.0-

Table. Description of Study Measures

Epigenetic BMI	Epigenetic BMI was computed on the basis of an epigenome-wide DNAm association study of adult BMI.[11] Using the summary statistics of the associations between DNAm sites and adult BMI, we created 1 methylation score per person per time point (ie, ages 9 and 15 years for FFCW) by summing the product of the weight and the individual β estimate for each individual at each of the 278 DNAm sites significantly associated ($P < 1 \times 10^{-7}$) with BMI. Importantly, these composite measures are not constructed from individual epigenetic modifications that are known to be causally related to BMI. Rather, they serve as statistical markers of otherwise unobservable epigenetic processes that are correlated with BMI.
	To examine the potential role of SNVs at DNAm sites, we computed epigenetic BMI after removing all 24 815 gap probes, which were determined by finding methylation probes that are correlated with genomic data. The gap-corrected epigenetic BMI was perfectly correlated with the original score because no gap probes were found in the score, suggesting that these scores are not simply substitutes for genetic variation.
	Epigenetic BMI was residualized for technical artifacts and cell composition (array, slide, batch, saliva-based cell composition estimates[33]) and then standardized.
	Analyses of duplicate samples suggested moderate reliability of epigenetic BMI profiles (FFCW: 216 replicates, ICC = 0.67; TTP: 15 replicates, ICC = 0.43).
BMI	We measured BMI from in-laboratory measurements (TTP) or in-home by an interviewer (FFCW) of height and weight transformed to sex- and age-normed z scores according to the method published by the US Centers for Disease Control and Prevention.[18]
SES	Family SES composites were computed as the average of standardized parent educational attainment and standardized, log-transformed income in both cohorts.
Puberty	Pubertal development[19-21] and tobacco exposure[22] have been associated with early-life disadvantage, as well as differential DNAm patterns.[9,22,23] We therefore consider these factors in our analysis.
	In TTP and FFCW, we measured pubertal development using children's self-reports on the Pubertal Development Scale.[39] The scale assesses the extent of development across 5 sex-specific domains (for both: height, body hair growth, skin changes; for females: onset of menses, breast development; for males: growth in body hair, deepening of voice). A total pubertal status score was computed as the average response (1 = Not yet begun to 4 = Has finished changing) across all items. Pubertal development was residualized for age, sex, and an age by sex interaction.
Tobacco exposure	We measured tobacco exposure from (1) participant self-report of tobacco use (no reported use for FFCW at age 9 years), (2) a whole-genome DNAm smoking score (DNAm-smoke, see below),[23] and (3) for FFCWS only, if the mother reported smoking during pregnancy.
DNAm scores of smoking	DNAm scores of smoking were computed on the basis of an epigenome-wide association study of adult smoking. Using the summary statistics of the associations between DNAm sites and adult smoking, we created 1 methylation score per person per time point (ie, ages 9 and 15 years for FFCW) by summing the product of the weight and the individual β estimate for each individual at each of the DNAm sites significantly associated ($P < 1 \times 10^{-7}$) with smoking. DNA smoke score was residualized for technical artifacts and cell composition (array, slide, batch, saliva-based cell) estimates[24] and then standardized.

Abbreviations: BMI, body mass index; DNAm, DNA methylation; FFCW, Future of Families and Child Well-Being study; ICC, intraclass coefficient; SES, socioeconomic status; SNV, single nucleotide variant; TTP, Texas Twin Project.

Figure 1. Associations Between Epigenetic Body Mass Index (BMI) and Measured BMI

Cross-sectional associations between scaled epigenetic BMI and measured BMI. Results are presented for 3 samples: 8- to 18-year-old children from the Texas Twin Project (TTP) and 9-year-old children and 15-year-old children from Future of Families and Child Well-Being (FFCW) study (FFCW 9 y; FFCW 15 y). Epigenetic BMI and BMI z scores were scaled in the full sample of each study and time point (A). Within monozygotic twin-pair associations between scaled epigenetic BMI and measured BMI, results were based on 183 monozygotic twin pairs from TTP (B). Association of within-person longitudinal changes in scaled epigenetic BMI and within-person change in BMI from age 9 years to age 15 years. Results based on 1904 longitudinal observations from FFCW (C).

4.2 (The R Project), Mplus 8 (Muthén and Muthén), and Stata 17 (Stata Corp) were used.

Results

Analysis 1: BMI Gradients Were Reproduced in Children's Salivary Epigenetic BMI

In a multiple regression model where BMI z scores were regressed on epigenetic BMI (**Figure 1**A), epigenetic BMI was significantly associated with BMI in 8- to 18-year-olds from the TTP (Pearson r = 0.50; 95% CI, 0.42-0.59), FFCW 9-year-olds (r = 0.36, 95% CI, 0.31-0.40), and FFCW 15-year-olds (r = 0.41; 95% CI, 0.36-0.45). The association between epigenetic BMI and BMI remained after adjustment for race and ethnicity, pubertal development, or indices of tobacco exposure (self-reported tobacco use in the TTP, maternal report of smoking during pregnancy in the FFCW, and DNAm indicator of tobacco exposure in both samples), which were included as statistical controls (eTable 2 in Supplement 1). Compared with a model with only these covariates, the ΔR^2 for epigenetic BMI was 24.3% in TTP, 9.5% in FFCW 9-year-olds, and 13.6% in FFCW 15-year-olds.

Analysis 2: Longitudinal Analysis Finds That Epigenetic BMI Was Stable Across Adolescence but Still Tracks Changes in BMI

Epigenetic BMI measured at age 9 years was correlated with epigenetic BMI measured at age 15 years (standardized regression coefficient [b] = 0.63; 95% CI, 0.60-0.67). In the fixed-effects regression model using longitudinal FFCW data (Figure 1C; eTable 3 in Supplement 1), within-person variation in epigenetic BMI from ages 9 to 15 years was associated with greater longitudinal increases in phenotypic BMI (b = 0.13; 95% CI, 0.07-0.20), even after adjusting for longitudinal changes in socioeconomic status (SES) and pubertal development. Epigenetic BMI in the fixed-effects model explained 16% of the between-person variance in BMI but 2% of the variance in within-person change. As a negative control, within-person epigenetic BMI from ages 9 to 15 years was unassociated with changes in phenotypic height (b = 0; 95 CI, −0.8 to 0.09).

In the bivariate random intercept cross-lagged panel model, there was evidence of a bidirectional association between epigenetic BMI and BMI (**Figure 2**; eFigure 1 and eTable 4 in Supplement 1): age 9 years' BMI was associated with age 15 years' epigenetic BMI (b = 0.11; 95% CI, 0.08-0.14) above and beyond age 9 years' epigenetic BMI, and, in reverse, age 9 years' epigenetic BMI was associated with age 15 years' BMI (b = 0.06; 95% CI, 0.03-0.10), above and beyond age 9 years' BMI.

Analysis 3: Epigenetic BMI Tracks Differences in BMI Between Monozygotic Twins

Consistent with previous work showing that DNAm is influenced by genetic variation, in the co-twin control analysis, the heritability of epigenetic BMI was estimated to be 46% (95% CI, 21%-71%) and the genetic correlation (rA) between epigenetic BMI and measured BMI was moderate (rA = 0.33, 95% CI, 0.17-0.50). However, the correlation between the E components of variation in DNAm and phenotypic BMI (rE), which reflects the extent to which identical twins who differ from their co-twins in epigenetic BMI show corresponding differences in their BMI, was also positive and significant (eTable 5 in Supplement 1; see Figure 1B; rE = 0.24; 95% CI, 0.10-0.37). Thus, among individuals who have been matched on nuclear DNA sequence, as well as on the background environmental

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Figure 2. Cross-Lagged Model of Epigenetic Body Mass Index (BMI) and BMI in the Future of Families and Child Well-Being Study

Var ε_{B9} = 1.3 (0.04); Var ε_{B15} = 0.6 (0.02)
Var ε_{EB9} = 1.0 (0.03); Var ε_{EB15} = 0.6 (0.03)
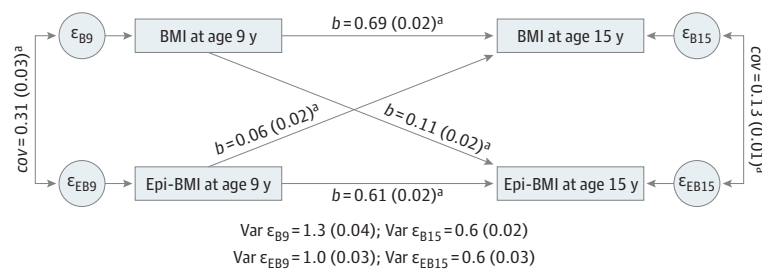
BMI is the US Centers for Disease Control and Prevention z score for BMI for age. Epigenetic BMI (Epi-BMI) was residualized for cell distributions and technical artifacts and normalized with a mean = 0, SD = 1. Coefficients not shown are controls that influence age 9 years' BMI and age 9 years' epigenetic BMI, including self-reported race, sex assigned at birth, socioeconomic status at

birth, and if mom smoked while pregnant (see eTable 6 in Supplement 1). SDs of the residual error variances of BMI and epigenetic BMI are in parenthesis after their variance estimate. Cov indicates covariance; var, variance.

[a] P < .05

Figure 3. Socioeconomic Inequalities in Children's Epigenetic Body Mass Index (BMI) Profiles
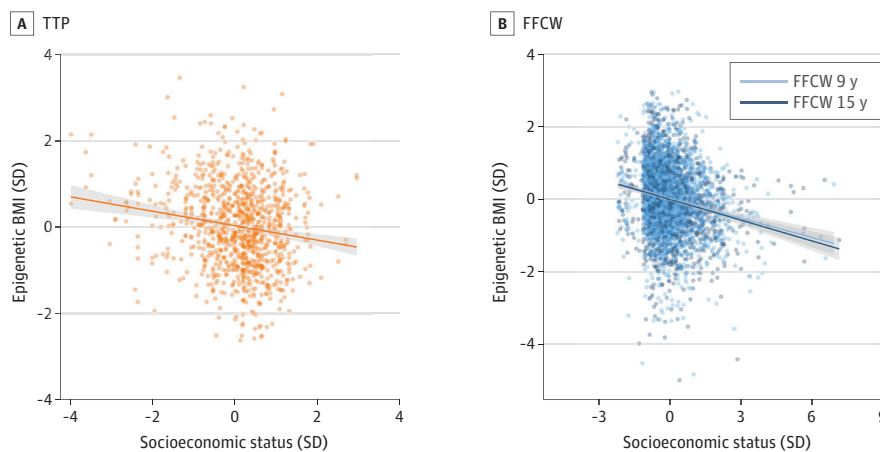
Cross-sectional associations between scaled family-level socioeconomic status and salivary epigenetic BMI. Results are presented for 3 samples: A, data from 8- to 18-year-old children from the Texas Twin Project (TTP) and B, data from 9-year-old children and 15-year-old children from Future of Families and Child Well-Being (FFCW) study (FFCW 9 y; FFCW 15 y). Socioeconomic status z scores and epigenetic BMI were scaled in the full sample of each study and time point.

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factors shared by twins raised in the same family, variation in epigenetic BMI continues to be associated with BMI. The moderate heritability of epigenetic BMI indicates that, as with phenotypic BMI, there were both genetic and environmental sources of variation in methylation. The positive genetic and nonshared environmental correlations between epigenetic BMI and phenotypic BMI indicate that it is both these genetic and environmental sources of variation in epigenetic and phenotypic BMI that are linked, which is consistent with a causal basis for the observed association. Additionally, consistent with results from previous studies in adults,[29-31] salivary epigenetic BMI provided complementary information compared with measured genetic variants associated with BMI (ie, polygenic indices of BMI; eResults and eTable 6 in Supplement 2).

Analysis 4: Children From Lower Socioeconomic Status Show Higher Epigenetic BMI

Epigenetic BMI was significantly associated with family-level SES, measured using composites of parental income and education (**Figure 3**; eTable 7 in the Supplement). Results from the TTP sample were: b = −0.24; 95% CI, −0.34 to −0.13; results from the FFCW age 9 years group: b = −0.17; 95% CI, −0.22

to −0.13; and FFCW age 15 years group: b = −0.19; 95% CI, −0.23 to −0.14.

In both cohorts, even among children of comparable body size, pubertal development, and tobacco exposure, children from lower SES homes showed higher epigenetic BMI (TTP: b = −0.13; 95% CI, −0.22 to −0.03; FFCW age 9 years group: b = −0.15; 95% CI, −0.19 to −0.11; FFCW age 15 years group: b = −0.14; 95% CI, −0.18 to −0.90) (eTable 7 in Supplement 1).

Analysis 5: Children From Marginalized Racial and Ethnic Groups Show Higher Epigenetic BMI

In TTP and FFCW, African American/Black and Latinx children had significantly higher epigenetic BMI compared with White children (eTable 8 in Supplement 1). Notably, epigenetic BMI was significantly associated with BMI across all the 3 socially constructed racial and ethnic groups in subgroup analyses where BMI z scores were regressed on DNAm BMI within each group (eTable 9 in Supplement 1).

African American/Black and Latinx children tended to be exposed to higher rates of socioeconomic disadvantage compared with White children and this pattern has previously been observed in these cohorts.[14,32] African American/Black com-

Figure 4. Cross-Lagged Model of Socioeconomic Status (SES) and Epigenetic Body Mass Index (BMI) Profiles in the Future of Families and Child Well-Being Study

Var ε_{S9} = 0.3 (0.01); Var ε_{S15} = 0.2 (0.01)
Var ε_{EB9} = 1.0 (0.03); Var ε_{EB15} = 0.6 (0.02)
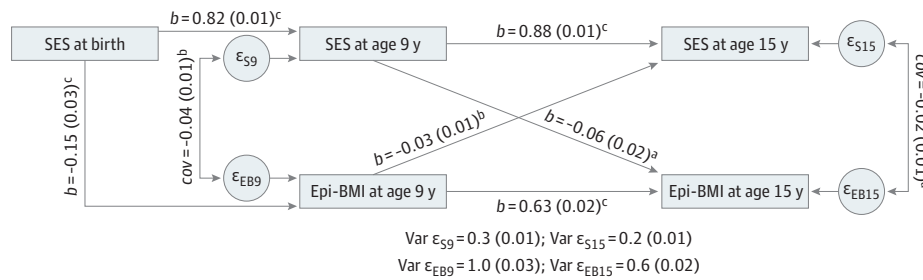
Epigenetic BMI (Epi-BMI) was residualized for cell distributions and technical artifacts. SES and epigenetic BMI are normalized with a mean = 0, SD = 1. Coefficients not shown are controls that influence age 9 years SES and age 9 years epigenetic BMI, including self-reported race, sex assigned at birth, and if mom smoked while pregnant (see eTable 10 in Supplement 1). SDs of the residual error variances of SES and epigenetic BMI are in parenthesis after their variance estimate. Cov indicates covariance; var, variance.

[a] $P < .05$
[b] $P < .01$
[c] $P < .001$

pared with White group differences in epigenetic BMI were statistically accounted for by differences in socioeconomic disadvantage in TTP and FFCW (eTable 8 in the Supplement) and Latinx compared with White group differences in epigenetic BMI were fully statistically accounted for by differences in socioeconomic disadvantage in TTP and were substantially reduced in FFCW (though significant differences remained).

Analysis 6: Epigenetic BMI Reflects Socioeconomic Conditions at Birth

Changes in SES and changes in BMI between 9 and 15 years were not correlated ($b = −0.06$; 95% CI, −0.15 to 0.04; eTable 10 in Supplement 1). However, SES remained highly stable over time ($b = 0.88$; 95% CI, 0.86-0.90). Given the stability of SES over child development, the final analysis estimated a random intercept cross-lagged panel model to test whether SES at birth, at age 9 years, and age 15 years was associated with epigenetic BMI at ages 9 and 15 years. SES at birth was associated with epigenetic BMI at age 9 years ($b = −0.15$; 95% CI, −0.20 to −0.09) (Figure 4; eFigure 2 and eTable 11 in Supplement 1). As epigenetic BMI is highly stable from ages 9 to 15 years ($b = 0.63$; 95% CI, 0.60-0.67), this suggests that very early-life SES may have a critical influence on lifetime epigenetic scores.

Discussion

Leveraging twin and longitudinal study designs, we examined (1) whether epigenetic BMI previously developed in adult blood samples is a valid biomarker of children's BMI when measured in saliva DNAm and (2) whether child epigenetic BMI is sensitive to social determinants of health in 2 sociodemographically diverse pediatric cohorts. We found that epigenetic BMI captured appreciable variance in concurrent BMI z scores, with effect sizes of a similar magnitude to what has been reported in adults.[7,9] The $\Delta R2$ for epigenetic BMI was 24.3% in TTP, 9.5% in FFCW age 9 years, and 13.6% in FFCW age 15 years after accounting for age, sex, race and ethnicity, pubertal development, and indices of tobacco exposure. Moreover,

epigenetic BMI was higher in children from socioeconomically disadvantaged homes and in children from marginalized racial and ethnic groups, with effect sizes of a similar magnitude to what has been reported for a DNAm measure of the pace of biological aging.[12,14]

Our results validate research that applies epigenetic measures of aging-related health developed in adult blood samples to pediatric saliva samples. Perhaps counterintuitively, this cross-tissue extension yielded stronger associations than has previously been found using blood samples in pediatric studies. Reed et al[31] reported that DNAm measured in blood captured only 1% to 3% of the variance in child BMI and was not prospectively associated with future BMI.[33] In contrast, we found that salivary epigenetic BMI was both a leading and lagging indicator of BMI change. Thus, the current results are encouraging, as saliva is more feasible to collect than blood in large numbers of participants. Our results contribute to a growing body of evidence that salivary epigenetic profiles of biological aging, physiological decline, health behaviors, and mortality can yield useful biomarkers that are sensitive to social inequalities and are a leading indicator of future health-relevant phenotypes.

Moreover, 3 of our findings are in line with the developmental origins of health and disease hypothesis and theories of epigenetic regulation of later life health.[2,3] First, we observed social stratification of epigenetic BMI using weights developed in adult samples, which indicates a molecular link between childhood social conditions and adult health. Second, epigenetic BMI was highly stable across adolescence, which suggests a substantial amount of between-person variation arises earlier in the life course. Third, we found that socioeconomic contexts at birth relative to concurrent socioeconomic contexts in childhood and adolescence was most strongly associated with epigenetic BMI in childhood and adolescence.

There has recently been a paradigm shift in aging research that anchors the onset of damage accumulation to the prenatal period as opposed to later in the life course after the completion of development and the onset of reproductive age.[34] Early ontogenetic development is especially sensitive

to environmental contexts, given the rapid pace of fetal development and high developmental plasticity. Experiences during this period appear to exert lasting effects on epigenetic predictors of aging-related health in older adults.[35] Intriguingly, our twin analyses found that epigenetic BMI reflected differences in BMI between monozygotic twins. This suggests that salivary epigenetic predictors of health are sensitive to either (1) prenatal and postnatal exposures that differ between monozygotic twins and affect body mass or (2) developmental idiosyncrasy in body mass development.

Limitations

We acknowledge limitations of our work. First, our results are limited by observational associations with socioeconomic contexts. It remains to be seen whether epigenetic measures are sensitive to experimental manipulations in socioeconomic resources in real-time, such as cash transfers in early childhood.[36] Second, our measures of social inequality were limited to household income, parental education, and racial and ethnic social identities. Future studies could examine environmental effects at different scales (eg, family, neighborhood, state) and across developmental epochs, including prenatal and birth factors, on epigenetic BMI. Third, epigenetic BMI was developed on the basis of a discovery sample of European and/or Indian Asian ancestry adults, which might be missing DNAm

sites of high relevance to high BMI in populations of distal ancestries.[9] Lastly, participants in our samples are still young. Thus, our findings are limited by not being able to examine epigenetic prediction of later-life health.

Conclusions

Social scientists have long argued that because adult health and mortality are shaped by childhood conditions, "economic and educational policies that are targeted at children's well-being are implicitly health policies with effects that reach far into the adult life course."[2] Evaluating the long-term health impact of childhood interventions and policies, however, is challenged by just how long the long arm of childhood is. Efforts to improve childhood living conditions could take decades to bear the fruit of reduced mortality and morbidity. The current study, by showing that an epigenetic measure developed in adults is a valid biomarker of childhood BMI, builds on previous work showing that epigenetic measures can be a molecular bridge between childhood and adulthood. It will be valuable for future studies assessing the impact of social policies in childhood to incorporate DNAm measures as outcomes that are potentially informative about future health payoffs.

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