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Maternal prenatal social experiences and offspring epigenetic aging from birth to mid-childhood

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Abstract

Purpose: Investigate associations of maternal social experiences with offspring epigenetic age acceleration (EAA) from birth through mid-childhood among 205 mother-offspring dyads of minoritized racial and ethnic groups.

Methods: We used linear regression to examine associations of maternal experiences of racial bias or discrimination (0=none, 1–2=intermediate, or 3+=high), social support (tertile 1=low, 2=intermediate, 3=high), and socioeconomic status index (tertile 1=low, 2=intermediate, 3=high) during the prenatal period with offspring EAA according to Horvath's Pan-Tissue, Horvath's Skin & Blood, and Intrinsic EAA clocks at birth, 3 years, and 7 years.

Results: In comparison to children of women who did not experience any racial bias or discrimination, those whose mothers reported highest levels of racial bias or discrimination had

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Declaration of interests

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lower Pan-Tissue clock EAA in early (−0.50 years; 90% CI: −0.91, −0.09) and mid-childhood (−0.75 years; −1.41, −0.08). We observed similar associations for the Skin & Blood clock and Intrinsic EAA. Maternal experiences of discrimination were not associated with Pan-Tissue EAA at birth. Neither maternal social support nor socioeconomic status predicted offspring EAA.

Conclusions: Children whose mothers experienced racial bias or discrimination exhibited slower EAA. Future studies are warranted to confirm these findings and establish associations of early-life EAA with long-term health outcomes.

Keywords

Epigenetic age acceleration; experiences of discrimination; social exposures; prenatal period; maternal-offspring dyads; cohort study

INTRODUCTION

The aging epidemic has forged interest in patterns and determinants of aging [1–3]. Recently, social determinants of health have risen to the forefront as important drivers of age-related non-communicable conditions [4], with evidence in humans [5,6], non-human primates [7–9] and rodents [8,10] revealing an indisputable link between unfavorable social experiences and chronic disease risk. The effect of social experiences on health is hypothesized to operate, in part, through epigenetic mechanisms [11–13]. Of relevance to aging research are genome-wide changes in DNA methylation that occur as individuals get older [14–17]. Epigenetic clocks are functional biomarkers of developmental and aging processes [18–20] that capitalize on age-related changes to DNA methylation [21,22]. One biomarker of recent interest is epigenetic age acceleration (EAA) – i.e., the estimated difference between epigenetic age and chronological age – as it outperforms other molecular markers of aging, including telomere length [23] and is a strong predictor of morbidity and mortality [24–28].

Studies in adults have found that adverse social experiences predict higher EAA [29–32] with stronger effects observed for experiences occurring earlier vs. later in life [30,33]. Our group recently showed that EAA starts before birth [34], pointing toward the importance of considering how prenatal exposures shape the aging process. To date, only a handful of studies have examined the relationship between maternal social or psychosocial experiences and offspring epigenetic aging. The findings are inconsistent, with some studies indicating faster offspring epigenetic aging following unfavorable maternal experiences, and others suggesting the opposite. In a combined analysis of two cohorts in the Netherlands and Singapore, McGill et al. reported positive associations of maternal prenatal anxiety with higher EAA among male offspring through age 4 years [35]. Similarly, in the U.K.-based ALSPAC cohort, maternal adverse childhood experiences (ACEs) predicted higher offspring EAA at birth, again primarily in males [36]. On the other hand, in the Finnish PREDO Study, Suarez et al. found that maternal history of pre-pregnancy depression and higher antenatal depressive symptoms were each associated with lower epigenetic gestational age at birth in both sexes [37]. In the California Salinas Valley CHAMACOS study, Nwanaji-Enweren et al. reported both positive and negative associations of maternal ACEs with offspring epigenetic age acceleration at ages 7, 9, and 14 years, with similar patterns by sex, and also noted that maternal ACEs predicted longer offspring telomere length, indicative of

slower biological aging [38]. While the inconsistent findings may reflect differences in specific maternal exposures of interest, method of assessing epigenetic age, and study population characteristics, they also highlight a need for additional research in this area.

In this exploratory pilot study, we investigated associations of maternal social experiences with offspring EAA from birth through mid-childhood among 205 mother-offspring pairs of minoritized racial and ethnic groups. Specifically, we sought to examine associations of maternal experiences of racial bias or discrimination, social support, and indicators of socioeconomic disadvantage during the prenatal period with three measures of EAA at birth and across early and mid-childhood: (1) Horvath's Pan-Tissue clock, (2) Horvath's Skin & Blood clock, and the (3) Intrinsic EAA (IEAA) clock. We focus only on mother-offspring pairs from minoritized groups considering the increasingly recognized importance of experiences of racial bias or discrimination on a range of maternal/child outcomes [39,40] and to reduce the possibility of exposure misclassification among white women who experience bias or discrimination for non-race-related reasons. We hypothesized that maternal experiences of racial bias or discrimination, lower social support, and socioeconomic disadvantage will be associated with persistent differences in offspring EAA across early-life.

MATERIALS AND METHODS

Study population

This analysis used data from Project Viva, a pre-birth cohort of mother-child pairs recruited 1999–2002 from multi-specialty clinics in Massachusetts (Atrius Harvard Vanguard Medical Associates [41]. Of the 2,128 enrolled mother-child pairs, 708 had high-quality data on whole-genome DNA methylation in cord blood (n=485) and blood collected from offspring in early childhood (age 3–6 years, n=120) or mid-childhood (age 6–10 years, n=460). Given our interest in maternal experiences of racial bias or discrimination, we restricted the analysis to mother-offspring pairs of minoritized populations based on the mothers' self-reported race and ethnicity, which we view as a social construct as opposed to a form of biological determinism [40]. At enrollment, we asked mothers, "Which of the following best describes your race or ethnicity?" Mothers had a choice of one or more of the following mutually exclusive racial/ethnic groups: Hispanic or Latina, white or Caucasian, Black or African American, Asian or Pacific Islander, American Indian or Alaskan Native, and Other (please specify). For the participants who selected 'Other,' we compared the specified responses to the US census definition for the other five race and ethnicities and reclassified them where appropriate. If a participant chose more than one racial or ethnic group, we classified them as ">1 racial or ethnic group." For this analysis, we excluded white mothers and used four racial/ethnic categories: "Black", "Hispanic," "Asian" and "More than 1 race or other." The analytic sample comprised 205 mother-offspring dyads and with DNA methylation data in cord (n=126), early childhood (n=25; range 3–6 years), and mid-childhood blood (n=149; range 6–11 years). Fifteen children contributed DNA methylation data at all three time-points.

Exposure: maternal social experiences

Experiences of discrimination (EOD)—At the early pregnancy visit (~10 gestational weeks), women reported experiences of racial bias or discrimination via an adapted version [39] of the validated Experiences of Discrimination (EOD) measure [42]. The questionnaire comprises eight questions inquiring on lifetime experiences of any racism, discrimination, or bias. Participants responded 'Yes' or 'No' to the prompt 'I have experienced unfair or bad treatment because of my race or ethnicity' for each of eight different situational domains: at school, getting hired or getting a job, at work, getting housing, getting medical care, getting service in a store or restaurant, on the street or in a public setting, and from the police or in the courts. We summed 'Yes' responses to produce an EOD score for self-reported experiences of racial discrimination (range 0–8), with the total number of domains conceptualized as an indicator of overall exposure [42,43.] We categorized EOD responses as none (EOD=0), moderate (EOD=1–2), and high (EOD=3+) as previously done [39,42].

Social support—We assessed social support during the prenatal period using the Turner Support Scale [44], which comprises 10 questions that prompts the respondent to rank, on a scale from 1 (most support – i.e., strongly agree with statement about positive support) to 4 (least support – i.e., strongly disagree with statement about positive support), the amount of support and affection that they received from their partner (five questions) and family/friends (five questions). Women without a partner at the early pregnancy visit skipped the first five questions, resulting in minimum possible scores of 10 and 5 for partnered and unpartnered women, respectively; and maximum possible scores of 40 and 20 for partnered and unpartnered women, respectively. In the analysis we categorized women into tertiles, using separate cut-points for partnered and unpartnered women. We reversed ranked the social support score such that the lowest tertile corresponded with receipt of the lowest social support (least favorable) and the top tertile corresponded with the highest social support (most favorable).

Prenatal SES index—As an indicator of socioeconomic disadvantage, we used an SES index that was associated with differential epigenome-wide DNA methylation from birth through mid-childhood in this cohort [45]. Components of the index include maternal educational attainment, marital status, annual household income, and receipt of public assistance assessed via questionnaires at the early pregnancy visit. For the analysis, we assessed the index as an ordinal variable with the lowest tertile representing the lowest SES and the top tertile representing the highest SES.

Outcomes: epigenetic clocks and estimation of EAA

We extracted DNA using the PureGene kits (Qiagen, Valencia, CA) from cord blood leukocytes and nucleated red blood cells collected at delivery, and from peripheral leukocytes collected during early and mid-childhood. DNA extracted from buffy coat was bisulfite treated (EZ DNA Methylation-Gold Kit, Zymo Research, CA, USA). DNA methylation values were derived using the Infinium HumanMethylation450 BeadChip (Illumina, CA, USA) array [46], following a standard DNA methylation quantification protocol [47] that we published [45]. DNA methylation QA/QC procedures are described in the Supplemental Material.

Using DNA methylation data from each life stage (birth, early childhood, mid-childhood), we derived two epigenetic clocks developed for use in multi-ethnic populations, each with utility for estimating biological age across multiple life stages and tissue types: Horvath's Pan-Tissue clock [48,49] and the Skin & Blood clock [50]. Both clocks were developed using training data from cord blood and multiple tissue types including peripheral leukocytes collected from pediatric populations (<18 years), thereby facilitating comparability in estimates of epigenetic age across the multiple life stages of interest in this study. Details on derivation, QA/QC, and performance of these clocks in Project Viva are published [34] and in the Supplemental Material.

For the analysis, the outcome of interest is epigenetic age acceleration (EAA) – a continuous, normally-distributed variable estimated as the residuals obtained from regressing chronological age on epigenetic clock age. EAA can be negative, indicative of slower biological aging/development relative to the sample average; positive, indicative of accelerated biological aging/development, relative to the sample average; or approximately 0, indicating that a child's biological age is equivalent to the sample average. We calculated EAA based on the Pan-Tissue and Skin & Blood clocks, and additionally considered a third assessment of age-related immunological changes calculated from the Pan-Tissue clock, called Intrinsic Epigenetic Age Acceleration (IEAA) [51]. We chose to focus on EAA rather than epigenetic age because the former is independent of chronological age and has been linked to age-related outcomes later in life [24–28].

Covariates

Research staff collected information on maternal prenatal smoking and parity via questionnaires at the early pregnancy visit. We calculated gestational age at delivery using the date of the mother's last menstrual cycle prior to the index pregnancy or second trimester ultrasound where available, or if the estimates differed by >10 days. We calculated maternal pre-pregnancy body mass index (BMI; kg/m^2) using self-reported pre-pregnancy weight collected at enrollment and clinically-measured height. Prenatal medical records provided information on mode of delivery and offspring sex.

Data analysis

First, we assessed the relationship between the three maternal social exposures with offspring EEA, separately, during each life stage using linear regression. We included maternal prenatal smoking as confounders per expert recommendations for studies examining perinatal determinants of epigenetic endpoints [52] and offspring sex given known sex differences in DNA methylation.

Next, we considered EAA across early and mid-childlood as repeated outcomes using mixed-effects models with random intercepts and an unstructured corrrelation matrix. This approach is complementary to the above analysis, but more efficiently leverages longitudinal data by including all participants to contribute to the standard error of the model, so long as they have at least outcome measurement. In multivariable anlayses, we adjusted for maternal prenatal smoking and child sex (Model 1), followed by additional adjustment for EAA at birth to account for variation in biological age at birth (Model 2). Nota bene, we adjusted

for EAA at birth as a covariate rather than include it as part of the repeated measures outcomes as EAA assessed in cord leukocytes may not be comparable to EAA estimated from peripheral leukocytes during childhood.

In sensitivity analysis, we adjusted for cell type composition at the time of sample collection to ensure that associations are not completely driven by variation in cell type composition, acknowledging that it could be a mediator [53,54].

For all models, we used α=0.10 as the threshold for statistical significance. We selected a relaxed α due to the relatively small sample and correlated nature of the three maternal social exposures and three offspring EAA outcomes at three life stages. However, when interpreting results, we focus on consistency in the direction and magnitude of associations for the relationships of interest within and across life stages, rather than statistical significance. Analyses were conducted in R, version 4.3.0 [55] and SAS 9.4 (SAS Institute Inc., NC, USA).

RESULTS

Descriptive statistics

The average age of mothers at enrollment was 29.8±6.3 years. Forty-five percent of the women identified as Black, 24.4% as Hispanic, 15.1% as Asian, and 15.6% identified as multi-racial or 'other.' Most women (76.1%) were married/cohabiting. Forty-four percent graduated college and 35.4% had an annual household income >$70,000. Forty-six percent of offspring were female. Table 1 shows additional characteristics of the sample and the distribution of the maternal social exposures and offspring EAA.

Bivariate associations

Experiences of discrimination (EOD) and social support scores were inversely correlated (Pearson's R^2=−0.24; P=0.002), such that more EOD correlated with lower social support. Prenatal SES was mildly positively correlated with social support (Pearson's R^2=0.13; P=0.10). EOD and the prenatal SES index were uncorrelated (Pearson's R^2=−0.03; P=0.72).

Table 2 shows correlations among chronological and epigenetic age based on the Pan-Tissue and Skin & Blood clocks. All correlation coefficients were positive and increased in magnitude from low at birth (Pearson's R^2 0.08 to 0.19) to moderate at early (0.28 to 0.61) and mid-childhood (0.49 to 0.59).

Multivariable analysis

Supplemental Table 1 shows associations of maternal social experiences with offspring EAA, separately by life stage. We found an inverse association of maternal EOD with offspring EAA during early and mid-childhood, but no associations at birth. In comparison to children whose mothers reported no EOD, those born to women with EOD scores of 1–2 (−0.71 years, 90% CI: −1.18, −0.24) or 3+ (−0.50 years, 90% CI: −0.91, −0.09) had lower EAA in early childhood according to the Pan-Tissue clock. We noted similar inverse associations of EOD with EAA according to the Skin & Blood clock and IEAA during early childhood, and according to all three clocks during mid-childhood. On the other hand, we

did not observe consistent associations of social support or the prenatal SES index with EAA according to any of the clocks. We observed similar associations when assessing EAA longitudinally across early and mid-childhood. In comparison to children whose mothers reported no EOD, those whose mothers had highest EOD exhibited lower EAA across early and mid-childhood according to the Pan-Tissue clock (−0.69, 90% CI: −1.23, −0.13), Skin & Blood clock (−0.49, 90% CI: −0.91, −0.07), and IEAA (−0.58, 90% CI: −1.15, −0.01) (Table 3, **Model 1**). Adjustment for cord blood EAA did not change associations for the Pan-Tissue clock or IEAA (Table 3, **Model 2**).

Sensitivity analysis

Adjustment for cell type composition at the time of epigenetic age assessment did not change results (Supplemental Tables 2 and 3). Therefore, we focus on estimates from non-cell-type adjusted estimates from the main analysis to avoid overadjustment [56].

DISCUSSION

In this pilot study of 205 mother-offspring pairs of minoritized racial and ethnic groups, maternal experiences of discrimination corresponded with lower EAA in offspring across early (age 3 years) and mid-childhood (age 7 years). While these findings contrast with an adult literature indicating that unfavorable social experiences correlate with higher EAA [33,57–61], there could be differential implications of EAA before vs. after reproductive maturity. Indeed, our findings align with a recent study of Latino families in which Clausing et al. found that maternal experience of discrimination was related to lower epigenetic age measured in saliva of children [62]. Additionally, the broader construct of maternal psychosocial stress has been linked to lower offspring EAA at birth in the PREDO cohort [37]. The inverse association observed in this, and other studies may reflect life history trade-offs in which costs incurred during early-life accumulate and negatively affect future growth and somatic maintenance [63–66]. Still, several studies report findings in the opposite direction. For example, unfavorable prenatal experiences like pregnancy complications [67], prenatal anxiety [35], and maternal ACEs [38] are associated with higher offspring EAA during childhood and adolescence. Such inconsistencies emphasize a need for additional research in this area.

Of note, we did not find associations between any maternal exposures and EAA at birth. Beyond the possibility of no true association, this finding may reflect the fact that we used epigenetic clocks developed to assess epigenetic age across multiple life stages. Such clocks may be less sensitive to differences in gestational age than those developed to specifically assess epigenetic age in newborns [68–70]. Additionally, neither maternal social support nor the prenatal SES index predicted offspring EAA. The null results could be because this study took place in a mid- to upper-income population in eastern Massachusetts, resulting in a relatively narrow range of SES that may have limited our ability to detect associations. Moreover, we excluded white participants given a central focus on the experiences of racial discrimination which likely reduced variation in social experiences.

Strengths of our study include prospectively collected data in multi-ethnic mother-offspring dyads; assessment of the women’s lifetime experiences of racial bias or discrimination; and assessment of EAA using multiple clocks and across multiple sensitive periods of

development. Our study also has limitations. First, while we used epigenetic clocks developed from populations of diverse ancestries [48,50], the extent to which these clocks are appropriate for assessing epigenetic age at birth [70,71] and across early life is unknown [72]. Second, we were underpowered to assess sex-specific associations. Third, our small sample sizes likely limited statistical power to detect smaller effect sizes. Finally, we caution against extrapolating the results beyond the scope of the racial/ethnic groups in this analysis, which comprised mother-offspring pairs of minoritized populations.

Conclusions

In this study of mother-offspring pairs from minoritized racial and ethnic groups and of mid-to-high socioeconomic status, maternal experiences of racial bias or discrimination are associated with slower biological aging in offspring across early and mid-childhood. This finding is consistent with the theory that social stressors contribute to an intergenerational "embedding" of health disparities by slowing development during early-life [73]. Future studies are warranted to confirm our findings and assess the relationship between early-life EAA across multiple developmental stages with clinically-relevant outcomes or well-recognized biomarkers of aging. Additionally, considering evolutionary processes, including the adaptive significance of tempo of development, will elucidate explanations for why adverse social experiences compromise health over the lifecourse [74].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

EAA	Epigenetic age acceleration
EOD	experiences of discrimination
IEAA	intrinsic epigenetic age acceleration
SES	socioeconomic status

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Table 1

Background characteristics of 205 Project Viva mother-offspring pairs of minoritized racial/ethnic groups overall, and among subgroups with DNA methylation (DNAm) data at birth (n=126), and during early (n=25) and mid-childhood (n=149).

	Overall *n* = 205	**Cord blood DNAm data** *n* = 126	**Early childhood DNAm data** *n* = 25	**Mid-childhood DNAm data** *n* = 149
Sociodemographic and background characteristics				
Mother's age at enrollment (years)	29.8 ± 6.3	29.9 ± 6.1	30.9 ± 6.2	29.7 ± 6.4
Nulliparous at index pregnancy	43.4% (89)	45.2% (57)	36.0% (9)	43.6% (65)
Pre-pregnancy BMI	25.7 ± 5.9	25.4 ± 5.8	27.4 ± 6.8	25.7 ± 7.0
Prenatal smoking habits				
Never smoked	73.7% (151)	73.8% (93)	68.0% (17)	73.8% (110)
Former smoker	9.8% (20)	11.1% (14)	8.0% (2)	10.1% (15)
Smoked during pregnancy	16.6% (34)	15.1% (19)	24.0% (6)	16.1% (24)
Mother's race and ethnicity				
Black	44.9% (92)	38.9% (49)	32.0% (8)	49.0% (73)
Hispanic	24.4% (50)	26.2% (33)	24.0% (6)	22.8% (34)
Asian	15.1% (31)	16.7% (21)	28.0% (7)	13.4% (20)
>1 race/ethnicity or other	15.6% (32)	18.3% (23)	16.0% (4)	14.8% (22)
Married or cohabitating	76.1% (156)	77.8% (98)	76.0% (19)	73.2% (109)
Education level				
No college	20.5% (42)	17.5% (22)	24.0% (6)	21.5% (32)
Some college	34.1% (70)	34.1% (43)	28.0% (7)	35.6% (53)
College degree	24.4% (52)	25.4% (32)	20.0% (5)	25.5% (38)
Graduate degree	20.0% (41)	23.0% (29)	28.0% (7)	17.5% (26)
Annual household income				
≤$20,000	12.7% (23)	7.9% (8)	4.8% (1)	15.3% (20)
>$20,000 - $40,000	30.4% (55)	26.6% (30)	23.8% (5)	32.8% (43)
>$40,000 - $70,000	21.5% (39)	27.4% (31)	28.6% (6)	19.1% (25)
>$70,000	35.4% (64)	38.9% (44)	42.9% (9)	32.8% (43)
Receipt of public assistance	19.8% (36)	13.3% (15)	17.4% (4)	22.3% (29)
Gestational age at delivery (weeks)	39.4 ± 1.7	39.4 ± 1.8	38.8 ± 1.6	39.4 ± 1.7
Child is female sex	45.9% (94)	45.2% (57)	52.0% (13)	47.7% (71)
Social exposures				
Experiences of discrimination (EOD)				
Mean ± SD	2.1 ± 2.0	2.1 ± 2.0	1.7 ± 2.0	2.2 ± 2.1
Median	2.00	2.00	1.00	2.0
Min, Max	0, 8	0, 8	0, 7	0, 8
Social support score				
Women with a partner				

	Overall ***n* = 205**	**Cord blood DNAm data** ***n* = 126**	**Early childhood DNAm data** ***n* = 25**	**Mid-childhood DNAm data** ***n* = 149**
Mean ± SD	14.1 ± 4.0	13.9 ± 3.9	14.5 ± 3.6	14.4 ± 4.0
Median	13.0	13.0	13.5	13.0
Min, Max	9, 28	10, 28	10, 23	9, 27
Women without a partner				
Mean ± SD	6.8 ± 2.1	6.4 ± 2.2	5.0 [a]	7.0 ± 2.3
Median	6.0	5.0	5.0 [a]	6.0
Min, Max	5, 10	5, 10	5.0 [a]	5, 10
Prenatal SES index				
Mean ± SD	−0.56 ± 0.94	−0.58 ± 0.91	−0.79 ± 0.85	−0.60 ± 0.93
Median	−0.89	−0.87	−1.09	−0.99
Min, Max	−1.65, 1.53	−1.65, 1.49	−1.65, 1.13	−1.65, 1.53

Abbreviations: BMI - body mass index; DNAm - DNA methylation; SES - socioeconomic status

[a] *n* = 1, therefore no estimate of SD or range.

Table 2

Pearson's correlation coefficients (R^2) among chronological age, Horvath's Pan Tissue Clock, and Skin & Blood Clock at birth and during early (median age 3.1 y) and mid-childhood (median age 7.8 y) among 205 Project Viva mother-offspring pairs of minoritized racial/ethnic groups.

	Chronological age	Pan-Tissue	Skin & Blood
Birth (n = 126)			
Chronological age	1.00	0.08	0.14
Pan Tissue		1.00	0.19
Skin & Blood			1.00
Early childhood (n = 25)			
Chronological age	1.00	0.49	0.28
Pan Tissue		1.00	0.61
Skin & Blood			1.00
Mid-childhood (n=149)			
Chronological age	1.00	0.49	0.59
Pan Tissue		1.00	0.58
Skin & Blood			1.00

Table 3

Associations (β [90% CI]) of maternal experiences of discrimination, social support, and prenatal socioeconomic (SES) status index with offspring epigenetic age acceleration as repeated measures across early (median age 3.1 y) and mid-childhood (median age 7.8 y) among Project Viva mother-offspring pairs of minoritized racial/ethnic groups.

	Pan-Tissue	Skin & Blood	IEAA
Model 1			
Experience of discrimination	*n=141*	*n=141*	*n=141*
0 (lowest)	0.00 (Reference)	0.00 (Reference)	0.00 (Reference)
1-2	−0.40 (−0.94, 0.16)	−0.21 (−0.63, 0.21)	−0.31 (−0.88, 0.25)
3+ (highest)	**−0.69 (−1.23, −0.13)**	**−0.49 (−0.91, −0.07)**	−0.58 (−1.15, −0.01)
P-trend	**0.05**	**0.06**	0.10
Social support	*n=138*	*n=138*	*n=138*
Tertile 1 (lowest)	−0.48 (1.00, 0.04)	−0.18 (−0.57, 0.22)	−0.32 (−0.83, 0.19)
Tertile 2	−0.02 (−0.57, 0.53)	−0.20 (−0.62, 0.22)	0.12 (−0.42, 0.66)
Tertile 3 (highest)	0.00 (Reference)	0.00 (Reference)	0.00 (Reference)
P-trend	0.15	0.46	0.32
Prenatal SES index	*n=118*	*n=118*	*n=118*
Tertile 1 (lowest)	−0.35 (−0.93, 0.25)	0.08 (−0.35, 0.50)	−0.38 (−0.95, 0.20)
Tertile 2	0.00 (Reference)	0.00 (Reference)	0.00 (Reference)
Tertile 3 (highest)	−0.39 (−1.01, 0.25)	0.05 (−0.39, 0.50)	−0.41 (−1.01, 0.19)
P-trend	0.96	0.93	0.98
Model 2			
Experiences of discrimination	*n=72*	*n=72*	*n=72*
0 (lowest)	0.00 (Reference)	0.00 (Reference)	0.00 (Reference)
1-2	−0.62 (−1.32, 0.08)	−0.47 (−1.02, 0.09)	−0.61 (−1.38, 0.16)
3+ (highest)	**−1.06 (−1.75, −0.39)**	−0.47 (−1.01, 0.08)	**−0.90 (−1.66, −0.16)**
P-trend	**0.02**	0.20	**0.07**
Social support	*n=69*	*n=69*	*n=69*
Tertile 1 (lowest)	−0.38 (−0.99, 0.24)	0.20 (−0.32, 0.72)	−0.18 (−0.82, 0.46)
Tertile 2	0.39 (−0.31, 1.08)	−0.03 (−0.63, 0.56)	0.58 (−0.16, 1.30)
Tertile 3 (highest)	0.00 (Reference)	0.00 (Reference)	0.00 (Reference)
P-trend	0.36	0.55	0.67
Prenatal SES index	*n=61*	*n=61*	*n=61*
Tertile 1 (lowest)	0.17 (−0.56, 0.90)	−0.03 (−0.59, 0.53)	0.17 (−0.58, 0.92)
Tertile 2	0.00 (Reference)	0.00 (Reference)	0.00 (Reference)
Tertile 3 (highest)	0.20 (−0.57, 1.00)	**0.68 (0.09, 1.26)**	0.28 (−0.52, 1.11)
P-trend	0.97	0.10	0.86

Abbreviations: IEAA: Intrinsic epigenetic age acceleration. **Bolded** values indicate statistical significance at alpha = 0.10.

Model 1: Estimates are adjusted for prenatal smoking habits (never/former/current) and offspring sex.

Model 2: Model 1 + cord blood measure of epigenetic age acceleration.