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Early life socioeconomic factors and genomic DNA methylation in mid-life

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Epigenetic modifications may be one mechanism linking early life factors, including parental socioeconomic status (SES), to adult onset disease risk. However, SES influences on DNA methylation patterns remain largely unknown. In a US birth cohort of women, we examined whether indicators of early life and adult SES were associated with white blood cell methylation of repetitive elements (Sat2, Alu and LINE-1) in adulthood. Low family income at birth was associated with higher Sat2 methylation (β = 19.7, 95% CI: 0.4, 39.0 for lowest vs. highest income quartile) and single parent family was associated with higher Alu methylation (β = 23.5, 95% CI: 2.6, 44.4), after adjusting for other early life factors. Lower adult education was associated with lower Sat2 methylation (β = -16.7, 95% CI: -29.0, -4.5). There were no associations between early life SES and LINE-1 methylation. Overall, our preliminary results suggest possible influences of SES across the life-course on genomic DNA methylation in adult women. However, these preliminary associations need to be replicated in larger prospective studies.

Introduction

Growing research has implicated exposures and risk factors encountered in utero, infancy and childhood in the development of several adult chronic diseases, including cardiovascular diseases and cancer.[1-3] Epigenetic modifications such as DNA methylation may play a role in linking early life exposures to adult disease risk.[4-6] Lower levels of genomic or global DNA methylation contribute to genomic instability, and have been observed in human tumors,[7,8] as well as in white blood cells (WBC) (reviewed in ref. 6).

Early life social conditions, including parental socioeconomic status (SES), have been associated with chronic disease risk later in life,[9-11] as well as with adult smoking, obesity and metabolic and chronic inflammation biomarkers.[12-16,32] These disease endpoints and risk factors are also being increasingly mapped to measures of genomic DNA methylation in adulthood;[6] however, research on early life social influences on adult DNA methylation is only beginning to emerge. Two UK studies recently reported significant associations between DNA methylation and several measures of SES. One study used an array-based methodology to examine genome-wide methylation in relation to childhood and adult SES,[17] while the other study examined global DNA methylation patterns by adult SES only.[18] Here, we investigated whether adult genomic DNA methylation was associated with SES indicators across the lifecourse.

Results

Table 1 displays the means and 95% confidence intervals (CI) of each measure of genomic DNA methylation by exposure variables measured in life periods of birth, childhood, and young and middle adulthood. Higher mean levels of Sat2 were observed for lower maternal education and lower family income at birth. The mean level of Alu was also higher for single-parent compared with two-parent family structure through age 13. Based on these bivariable results, we focused our multivariable analyses of early socioeconomic environment on the associations between maternal education and family income at birth and Sat2, and on the association between family structure through age 13 and Alu. We began with examining the potential confounding effect of other early life factors, and then examined whether these associations were independent of adult SES.

In age-adjusted models, lower maternal education and family income continued to be associated with higher Sat2, but the association was only statistically significant for the lowest vs. highest quartile of family income when both variables were included in the model (β = 20.1, 95% CI: 0.9, 39.2; **Table 2**, Model 1). Maternal smoking during pregnancy [hereafter referred to as prenatal tobacco smoke (PTS)] and birth order were identified as early life factors that affected the associations of early life SES and Sat2. Further adjustment for PTS and birth order attenuated the association for maternal education, but had minimal

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Table 1. Univariable associations between lifecourse socioeconomic factors, early life maternal characteristics and repetitive element methylation, New York Women's Birth Cohort

	N	Sat 2 (n = 87)		Alu (n = 88)		LINE-1 (n = 89)	
		Mean	95% CI[a]	Mean	95% CI[a]	Mean	95% CI[a]
Self-reported race/ethnicity							
African American	28	87.2	(75.7, 98.7)	117.2	(103.1, 131.4)	169.2	(148.4, 190.0)
Hispanic	38	82.7	(73.0, 92.4)	101.4	(89.0, 113.7)	159.9	(142.0, 177.8)
White	23	82.4	(69.6, 95.1)	104.8	(89.2, 120.5)	168.4	(145.4, 191.4)
Maternal nativity							
US-born (excluding Puerto Rico)	52	84.4	(75.9, 92.8)	108.3	(97.7, 118.8)	167.4	(152.2, 182.6)
Foreign-born	37	83.6	(73.8, 93.3)	105.9	(93.3, 118.6)	161.6	(143.6, 179.7)
Maternal age at pregnancy							
< 25	39	77.0*	(67.5, 86.4)	103.7	(91.5, 115.8)	168.0	(150.4, 185.6)
≥ 25	50	89.5	(81.2, 97.8)	110.2	(99.4, 121.0)	162.7	(147.1, 178.2)
Maternal smoking in pregnancy							
Yes	32	76.9*	(66.4, 87.4)	104.2	(90.8, 117.6)	159.6	(140.1, 179.1)
No	56	88.4	(80.5, 96.3)	109.7	(99.5, 119.9)	167.8	(153.1, 182.6)
Birth order							
1st born	33	80.4**	(70.5, 90.3)	101.7	(88.4, 115.0)	163.6	(145.8, 181.3)
2nd born	24	76.3	(64.7, 87.8)	109.6	(94.0, 125.2)	159.6	(138.5, 180.8)
3rd born	16	83.6	(69.4, 97.8)	108.4	(89.3, 127.6)	151.8	(125.9, 177.7)
4th or later born	13	107.8	(92.1, 123.6)	119.1	(97.9, 140.3)	180.2	(151.5, 209.0)
Early life socioeconomic factors							
Family income at birth							
Lowest quartile 1	19	97.0*	(83.6, 110.3)	107.9	(89.9, 125.8)	170.7	(145.6, 195.9)
2	21	78.8	(66.4, 91.1)	110.9	(93.4, 128.4)	163.4	(139.5, 187.3)
3	21	83.2	(70.8, 95.6)	103.4	(86.3, 120.5)	155.3	(131.4, 179.2)
Highest quartile 4	21	72.9	(60.2, 85.6)	112.3	(95.2, 129.4)	177.2	(153.3, 201.1)
Parental occupation at birth							
Blue collar	53	86.7	(78.4, 95.0)	104.3	(93.9, 114.7)	166.5	(151.4, 181.7)
White collar	35	80.6	(70.5, 90.6)	112.6	(99.6, 125.6)	163.4	(144.8, 182.1)
Maternal education at birth							
< High school graduate	44	92.5**	(83.6, 101.3)	108.8	(97.4, 120.2)	167.2	(150.7, 183.8)
≥ High school graduate	45	76.1	(67.6, 84.7)	105.8	(94.4, 117.3)	162.8	(146.5, 179.2)
Family structure through age 13							
Single parent or other situations	20	87.9	(74.3, 101.5)	123.8**	(106.9, 140.8)	175.3	(150.8, 199.7)
Both parents present	69	82.9	(75.7, 90.1)	102.8	(93.9, 116.7)	162.0	(148.9, 175.2)
Adult socioeconomic factors							
Adult education							
≤ High school	13	79.9*	(63.2, 96.7)	96.1	(75.5, 116.7)	164.4	(134.4, 194.4)
Some post high school training	31	74.5	(64.1, 84.9)	104.9	(91.5, 118.3)	148.7	(129.3, 168.1)
College graduate	21	90.4	(77.5, 103.4)	101.1	(84.4, 117.7)	171.2	(147.6, 194.8)
Graduate education	24	93.0	(81.2, 104.8)	121.7	(106.5, 136.9)	181.0	(158.9, 203.1)
Adult income							
Lowest category 1	15	85.6	(70.4, 100.8)	104.8	(85.7, 124.0)	152.8**	(126.1, 179.4)
2	32	80.5	(69.7, 91.2)	110.9	(97.4, 124.5)	170.6	(152.3, 188.8)
3	20	77.1	(63.9, 90.3)	98.6	(81.1, 116.2)	137.3	(114.2, 160.4)
Highest category 4	21	95.3	(82.4, 108.1)	112.3	(95.2, 129.4)	194.2	(171.6, 216.7)
Adult occupation							
Blue collar	34	76.8*	(66.1, 87.4)	101.0	(88.2, 113.9)	166.1	(146.8, 185.5)
White collar	49	88.5	(79.9, 97.1)	110.0	(99.2, 120.7)	165.6	(149.5, 181.8)

[a]CI, confidence interval; *p < 0.1; **p < 0.05.

influence on the associations for family income at birth (β = 19.7 for lowest vs. highest quartile, 95% CI: 0.4, 39.0; **Table 2**, Model 2). Adult education reduced the magnitude of the association between family income at birth and Sat2 (β = 12.9 for lowest vs. highest quartile, 95% CI: -6.3, 32.0, **Table 2**, Model 3), but adult occupation did not have an appreciable influence on this association (β = 22.5 for lowest vs. highest quartile, 95% CI: 0.8, 44.1, **Table 2**, Model 4). Unlike the associations between lower maternal education and lower family income at birth and higher Sat2 methylation, lower adult education and blue collar

Table 2. Multivariable associations between maternal education and family income at birth and Sat2

	Model 1[a] n = 79		Model 2[b] n = 79		Model 3[b] n = 79		Model 4[b] n = 73	
	Beta	**(95% CI)**	**Beta**	**(95% CI)**	**Beta**	**(95% CI)**	**Beta**	**(95% CI)**
Maternal education at birth								
< High school vs. ≥ high school	10.7	(-2.5, 24.0)	3.0	(-10.6, 16.5)	6.5	(-6.7, 19.7)	3.4	(-11.6, 18.4)
Family income at birth								
Lowest vs. highest quartile	20.1	(0.9, 39.2)	19.7	(0.4, 39.0)	12.9	(-6.3, 32.0)	22.5	(0.8, 44.1)
Second vs. highest quartile	5.5	(-12.1, 23.2)	2.6	(-16.0, 21.3)	-0.8	(-18.8, 17.2)	3.0	(-16.9, 22.9)
Third vs. highest quartile	8.5	(-9.4, 26.4)	10.2	(-7.1, 27.4)	6.3	(-10.4, 23.1)	6.7	(-11.5, 24.8)
Adult education								
< College degree vs. ≥ college degree					-16.7	(-29.0, -4.5)		
Adult occupation								
Blue vs. white collar							-8.5	(-21.9, 4.9)

[a]Adjusted for age; [b]adjusted for age, prenatal smoke and birth order.

Table 3. Multivariable associations between family structure at age 13 and Alu

	Model 1[a] n = 88		Model 2[a] n = 81		Model 3[a] n = 76	
	Beta	**(95% CI)**	**Beta**	**(95% CI)**	**Beta**	**(95% CI)**
Childhood family structure (up to age 13)						
Single parent or other adult vs. both parents present	23.5	(2.6, 44.4)	23.8	(3.0, 44.6)	22.2	(1.0, 43.5)
Family income at birth						
Lowest vs. highest quartile	-9.3	(-33.2,14.6)	-12.7	(-37.1, 11.6)	-4.2	(-29.0, 20.7)
Second vs. highest quartile	-2.4	(-25.6, 20.8)	-3.6	(-26.7, 19.6)	1.0	(-22.1, 24.2)
Third vs. highest quartile	-14.8	(-37.9, 8.3)	-17.2	(-40.5, 6.1)	-17.8	(-41.3, 5.7)
Adult education						
< college degree vs. ≥ college degree			-11.0	(-28.0, 5.9)		
Adult occupation						
Blue vs. white collar					-12.1	(-29.2, 5.0)

[a]Adjusted for age.

occupation were associated with lower Sat2 methylation, with the association reaching statistical significance for adult education in the multivariable model (β = -16.7 for less than college degree vs. college or higher degrees, 95% CI: -29.0, -4.5, Model 3).

Family income at birth was the only childhood factor that affected the positive association between family structure at 13 and Alu, and was hence included, along with age, in the multivariable models for Alu (β = 23.5 for single vs. two parent family, 95% CI: 2.6, 44.4) (**Table 3**, Model 1). Adult SES indicators did not have significant associations with Alu and did not affect the associations between family structure and Alu (**Table 3**, Models 2 and 3).

Discussion

Individuals with more disadvantaged socioeconomic conditions generally have poorer health and higher risk for many diseases and related biological states.[19-22] Thus, we expected to observe lower genomic DNA methylation levels in individuals with lower socioeconomic circumstances. However, we observed associations for early life SES and methylation that were in the opposite direction in our study population of women in their middle adulthood, with women from the lowest childhood family income level and from single-parent families having higher methylation of Sat2 and Alu, respectively. In contrast, we found that higher adult SES, most notably highest educational attainment, was associated with lower DNA methylation of Sat2. The association between childhood SES and genomic DNA methylation has not been previously investigated and our preliminary results need to be further confirmed in larger prospective studies. Our results with respect to the associations for adult SES corroborate findings from another recent study of the UK pSoBid Cohort that showed global DNA hypomethylation, as measured in peripheral blood leukocytes using Methylamp, in participants with lower adult SES.[18]

Childhood and adult SES has also been recently examined in relation to whole-blood genome-wide methylation profiles using microarray analysis in 40 males from the 1958 British cohort.[17] This study identified a large number of differentially methylated promoters by childhood SES, which exceeded the number of promoters differentially methylated by adult SES. Furthermore, both higher and lower methylation levels were observed in childhood and adult SES, and there was minimal overlap in the promoters associated with childhood SES and adult SES. Although not definitive, this study, along with ours, provides some support for early life SES associations with adult DNA methylation changes

and suggests that these associations may be different from adult SES influences on adult DNA methylation.

Epigenetic epidemiology is in its early stages and our understanding of epigenetic processes underlying specific exposures and outcomes is currently limited. These limitations present particular challenges for complex constructs such as SES, which encompass multiple exposures and are often inadequately measured. Furthermore, the diversity of measures of DNA methylation makes comparison and interpretation of different results, both within and across studies, challenging. We have previously demonstrated significant variations in associations between different measures of genomic DNA methylation in blood (e.g., different repetitive elements, methyl acceptor, LUMA) and explanatory factors (e.g., PTS, race/ethnicity, family history of cancer).[23-25] Here, we observed associations between indicators of early life factors and Sat2 and Alu methylation, but did not find any significant associations for LINE-1. LINE-1 appears to be relatively stable over the lifecourse and shows little variations with age,[6,26,27] which may account for the lack of associations observed in this study.

Due to the exploratory nature of our study, we considered multiple early life factors, and our results must be interpreted with caution. Our study population was comprised of women only, and, thus, results may not be generalizable to men. Our tracing and enrollment of participants into the overall adult follow-up study was lower among individuals of lower childhood SES; however, blood collection in adulthood did not significantly vary by childhood or adult SES among those enrolled into the adult follow-up study. Despite these limitations, the prospectively collected data on multiple dimensions of SES provided rich and reliable data to examine early life factors and genomic DNA methylation in middle adulthood. In conclusion, we observed a few significant associations linking SES across the lifecourse to genomic DNA methylation in adult women. However, given the limited number of significant associations and the unexpected direction of the associations for early life SES, the results may reflect spurious influences and require replication in larger prospective studies.

Materials and Methods

Study population. This study draws on data from the New York Women's Birth Cohort, an adult follow-up study of former child participants in the National Collaborative Perinatal Project (NCPP), born between 1959 and 1963 in New York City (see refs. 28 and 29 for details). In an ancillary study of this cohort, we collected blood samples with sufficient DNA from 90 participants. All adult epidemiologic and blood samples were collected between 2001 and 2007 [mean age ± standard deviation (SD) at blood collection = 43.0 y; range: 38–46]. Participants without blood samples (n = 172) did not differ significantly from participants with blood samples on sociodemographic (age, race and SES), prenatal and maternal characteristics (e.g., maternal age, pregnancy weight gain and maternal smoking during pregnancy), infant and child anthropometry, and adult reproductive and lifestyle factors (e.g., parity, alcohol intake and smoking).

Early life data collection. Early life data were collected at the time of mothers' enrollment into the study while they were pregnant with the study participants and prospectively from delivery through age 7. Parental SES indicators at birth included maternal education at birth (< high school graduate, ≥ high school graduate), family income (in quartiles), and parental occupation (blue and white collar occupations). Parental occupation was primarily based on the father's occupation with maternal occupation used when father's occupation was missing. Maternal and birth characteristics collected at pregnancy or birth time points and considered for possible confounding variables included maternal nativity (born in the US vs. outside of the US including Puerto Rico), birth order, maternal age at pregnancy and PTS.

Adult data collection. Participants provided data on adolescence and adulthood periods via a questionnaire between 2001 and 2007. SES indicators included family structure up through age 13 (two-parent vs. single-parent or other households), participants' highest educational degree (high school or less, trade school or some college, college degree and graduate education), their current or most recent occupation (white and blue collar), and current household income (reported in 12 ordinal categories and categorized into four levels).

Adult methylation assays. We used a salting out procedure to extract genomic DNA from peripheral blood granulocytes and measured repetitive element methylation, blinded to epidemiologic exposure data. Aliquots of DNA (500 ng) were bisulfite treated with the EZDNA Methylation Kit (Zymo Research), which converted unmethylated cytosines to uracils while leaving methylated cytosines unmodified. The DNA was re-suspended in 20 μL of distilled water and stored at -20°C until further use.

We used the previously reported sequences of probes and forward and reverse primers of LINE1-M1, Sat2-M1 and Alu-M2 for analysis with the MethyLight assay.[30] We ran the assays on an ABI Prism 7900 sequence detection system (Life Technologies/Applied Biosystems). We used universal methylated DNA as a methylated reference (EMD Millipore Corporation), and an Alu-based control reaction (AluC4) to measure the levels of input DNA to normalize the signal for each methylation reaction. MethyLight data specific for the repetitive elements were expressed as a percentage of methylated reference (PMR) values.[31] We conducted each MethyLight in duplicate, using the mean as the PMR. Based on duplicate threshold cycle measures, the inter-assay coefficients of variation (CV) were 0.8 for LINE-1, 0.6 for Sat-2M1 and 0.9 for Alu-M2. We found good reproducibility as indicated by the intra- and inter-assay CV in the mean threshold cycles (Ct) of a pooled quality control sample of 1.2% and 1.9%, respectively. The percentage of methylation value is based on 4 Ct values using the formula: PMR = 100% × 2 exp - [Delta Ct (target gene in sample - control gene in sample) - Delta Ct (100% methylated target in reference sample - control gene in reference sample)]. The CV in percentage of methylation with laboratory values were 25.2% for samples analyzed on the same day and 28.5% for samples analyzed on different days.

Statistical analysis. We excluded data from participants with methylation levels greater than 3 standard deviations (SD) from the mean (n = 3, 2 and 1 for Sat2, Alu and LINE-1, respectively).

We performed linear regression analyses, beginning with bivariable associations between each early life and adult factors and each measure of repetitive element methylation. We focused our multivariable analysis on any indicators of childhood SES that had statistically significant bivariable associations with DNA methylation ($p < 0.1$). We then tested for any confounding effect from other early life factors (birth order, maternal nativity maternal age at pregnancy and PTS) by examining whether their inclusion in models affected the estimates of the association between early life socioeconomic environment and DNA methylation by > 10%. We examined whether adult factors influenced the associations between early life SES and DNA methylation, after adjusting for the confounding effect of other early life factors. All multivariable analyses were adjusted for age at adult follow-up. Our overall inferences were the same when using log-transformed measures of DNA methylation.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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