The time-dependent association between socioeconomic position and DNA methylation during childhood

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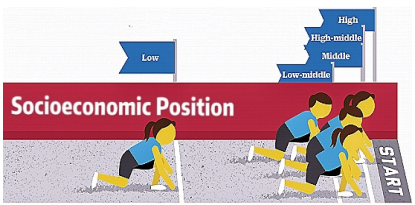
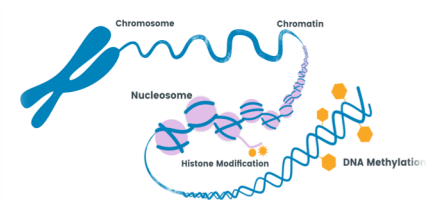
Background





- Low childhood socioeconomic position (SEP) is strongly associated with socioeconomic wellbeing in adulthood as well as lifelong physical and mental health risks.
- Growing evidence suggests that DNA methylation (DNAm) is a potential biological mechanism for how socioeconomic disadvantage "gets under the skin."
- However, few studies have examined the extent to which developmental timing, duration, and upwards/downwards mobility of SEP impact epigenome-wide DNAm profiles.

Study Question

Which life-course model explained the most variability (R^2) in age 7 DNAm?

(1) Sensitive period model:

The effect of low-SEP depends on the developmental time period of the exposure;

(2) Accumulation model:

The effect of low-SEP increases with the number of occasions exposed, regardless of timing;

(3) Mobility model:

Upward or downward change in SEP across development predicts DNAm patterns.

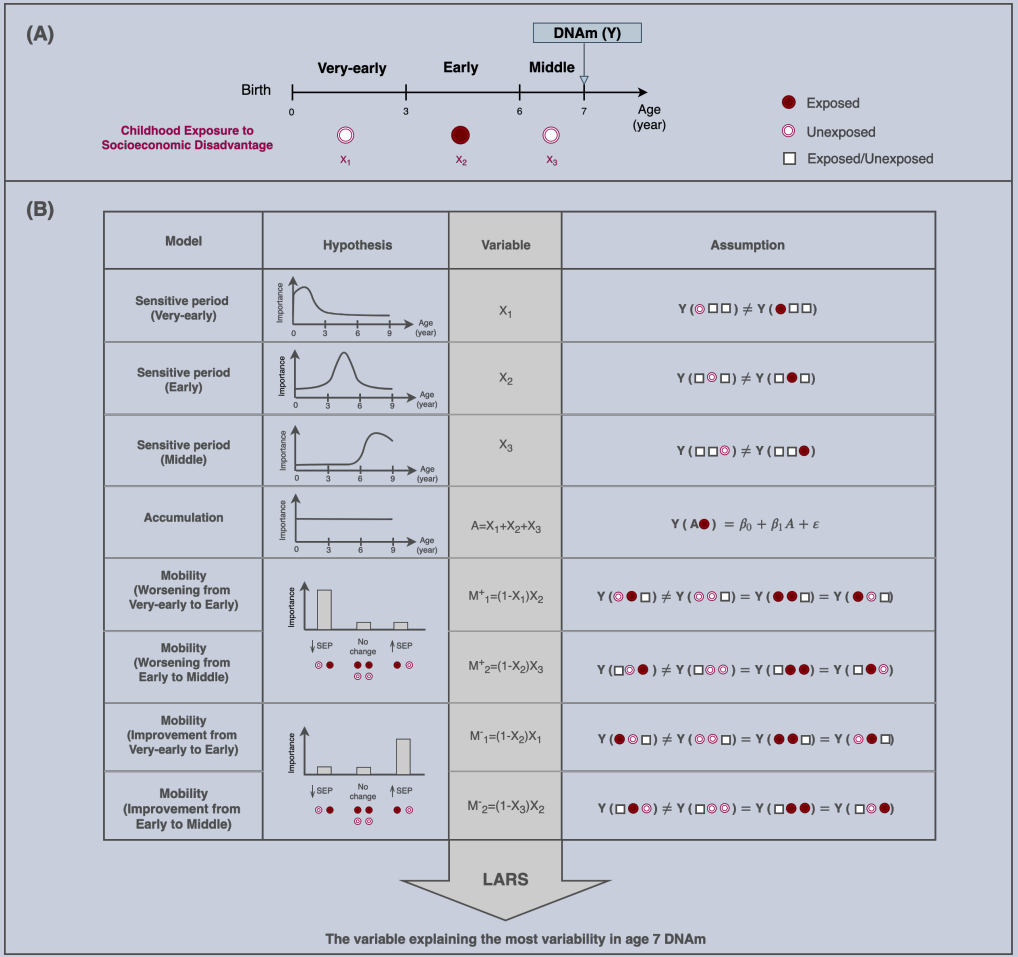


Figure 1. Study timeline (A) and SLCMA models (B)

Methods

Study sample

- Accessible Resources for Integrated Epigenomics Studies (ARIES), a subsample of mother-child pairs from the Avon Longitudinal Study of Parents and Children (ALSPAC; N=636-733).

Exposure assessment

- Six SEP measures: financial hardships, family income, income reduction, job loss, major financial problem, and neighborhood disadvantage.
- Assessed in *very-early childhood* (age 0-2), *early childhood* (age 3-5), and *middle childhood* (age 6-7).

Outcome assessment

- Epigenome-wide DNAm was measured from peripheral blood leukocytes at age 7 using Illumina Infinium Human Methylation 450k BeadChip microarray.

Statistical analysis

- Two-stage structured life course modeling approach (SLCMA, Figure 1):
  (1) Variable selection using Lease Angle Regression (LARS)
  (2) Effect estimate using multiple regression
- Each SEP measure was tested for three major theoretical models: *sensitive period*, *accumulation*, and *mobility* (except for job loss and income reduction not including *mobility*).
- Covariates adjusted in analysis: child race/ethnicity, child sex, child birth weight, maternal age, number of previous pregnancies, sustained maternal smoking during pregnancy, cell proportions, and child age at blood draw.
- Selective inference test was used to tested the null hypothesis that the variable selected is unassociated with the outcome, after taking model selection into account.
- Bonferroni correction was used to adjust for multiple testing across the epigenome.

Preliminary Results

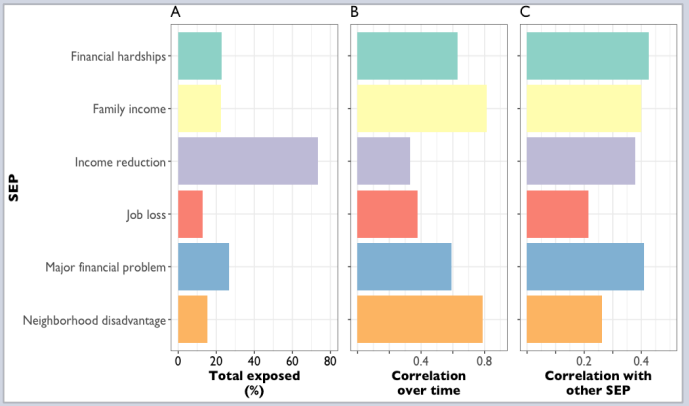


Figure 2. Exposure to socioeconomic disadvantage in the ARIES dataset

Figure 3. Number of CpGs with p<5e-5 by hypothesis for each SEP measure

Table 1. Results of the Structured Lifecourse Modeling Approach (SLCMA) for CpGs with p<1e-5

CpG	SEP	First hypothesis chosen by LARS procedure	DNAm in unexposed group (beta)	DNAm in exposed group (beta)	Increase in R^2	p-value	Effect estimate	SE	Lower 95%CI	Upper 95%CI	Nearest gene
cg07919128	Financial hardships	middle childhood	0.766	0.808	0.033	1.49E-06	0.043	0.009	0.026	0.061	MYO15A
cg25772299	(N=718)	accumulation	0.089	0.097	0.032	2.89E-06	0.005	0.001	0.003	0.007	GPC6
cg18607580		worsening (very-early to early)	0.930	0.910	0.031	3.55E-06	-0.020	0.004	-0.028	-0.012	BEND7
cg25420747		worsening (very-early to early)	0.840	0.754	0.029	6.15E-06	-0.087	0.018	-0.122	-0.051	KCNS3
cg10315800		improvement (very-early to early)	0.713	0.673	0.028	9.52E-06	-0.045	0.010	-0.064	-0.026	FAM120B
cg10993085	Family income	accumulation	0.919	0.928	0.035	3.02E-06	0.006	0.001	0.004	0.009	TNXB
cg26891645	(N=636)	very-early childhood	0.922	0.912	0.034	4.70E-06	-0.011	0.002	-0.015	-0.007	LOC649330
cg09448088		worsening (very-early to early)	0.916	0.865	0.032	6.51E-06	-0.051	0.011	-0.074	-0.029	MCF2L
cg22943762		accumulation	0.019	0.020	0.033	7.97E-06	0.001	0.000	0.000	0.001	SIX4
cg10785099		very-early childhood	0.982	0.980	0.032	9.03E-06	-0.002	0.000	-0.003	-0.001	KIF21B
cg15441230	Income reduction	very-early childhood	0.044	0.041	0.031	1.64E-06	-0.003	0.001	-0.005	-0.002	ELL3
cg00188971	(N=733)	middle childhood	0.928	0.937	0.028	5.26E-06	0.010	0.002	0.006	0.014	FTSJ1
cg08468371		early childhood	0.030	0.038	0.028	8.91E-06	0.008	0.002	0.005	0.011	SLC35G1
cg03764134	Job loss (N=689)	middle childhood	0.892	0.861	0.034	1.48E-06	-0.029	0.006	-0.041	-0.017	SNTG1
cg00462971	Major financial problem	worsening (very-early to early)	0.182	0.239	0.035	5.92E-07	0.058	0.011	0.037	0.079	XXYLT1
cg25035908	(N=733)	worsening (early to middle)	0.041	0.048	0.030	4.39E-06	0.007	0.001	0.004	0.009	DENND2C
cg04913057		worsening (early to middle)	0.017	0.021	0.028	6.53E-06	0.005	0.001	0.003	0.007	ETNK2
cg03692872	Neighborhood disadvantage	worsening (early to middle)	0.825	0.584	0.036	6.40E-07	-0.246	0.047	-0.339	-0.154	SPIRE2
cg11967332	(N=708)	improvement (very-early to early)	0.893	0.773	0.031	3.61E-06	-0.116	0.024	-0.162	-0.070	SLC25A24
cg12651540		worsening (very-early to early)	0.921	0.851	0.029	7.11E-06	-0.069	0.015	-0.098	-0.040	KIF7
cg23261103		improvement (very-early to early)	0.927	0.905	0.029	9.42E-06	-0.021	0.004	-0.030	-0.013	ZYG11B

Clinical & Policy Implications

- Our findings can contribute to an improved understanding of the biological consequences of socioeconomic disadvantage across different domains;
- The selected life-course theoretical model(s) can help optimize the timing of interventions or programs aimed at reducing the harms of socioeconomic disadvantage throughout childhood.

Next Steps

- Sensitivity analyses
- Sex-stratified analysis
- Compare results to a standard EWAS
- Enrichment analysis on genomic features and biological pathways
- Check mQTLs and eQTMs in the detected CpGs
- Check Methylation correlation across blood and brain for detected CpGs