Socially stratified epigenetic profiles are associated with cognitive functioning in children and adolescents

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Significance Statement

Children's cognitive functioning differs by dimensions of social inequality, such as class and race. Epigenetic mechanisms that regulate gene expression might be critically involved in the biological embedding of environmental privilege and adversity. We find that children growing up in more disadvantaged families and neighborhoods and from marginalized racial/ethnic groups exhibit higher chronic inflammation, lower cognitive functioning, and a faster pace of biological aging, as indicated by novel salivary DNA-methylation measures. These DNA-methylation measures of higher inflammation, lower cognitive functioning, and a faster pace of biological aging were, in turn, associated with performance on multiple cognitive tests. DNA-methylation measures might be useful as a surrogate endpoint in evaluation of programs to address the childhood social determinants of lifelong cognitive disparities.

Abstract

Children's cognitive functioning and educational performance are socially stratified. Social inequality, including classism and racism, may operate partly via epigenetic mechanisms that modulate neurocognitive development. Following preregistered analyses of data from 1,183 8- to 19-year-olds from the Texas Twin Project, we examined whether salivary DNA-methylation measures of inflammation (DNAm-CRP), cognitive functioning (Epigenetic-g), and pace of biological aging (DunedinPoAm) are socially stratified and associated with performance on tests of cognitive functions. We find that children growing up in more disadvantaged families and neighborhoods and children from marginalized racial/ethnic groups exhibit DNA-methylation profiles associated with higher chronic inflammation, lower cognitive functioning, and faster

pace of biological aging. These salivary DNA-methylation profiles were associated with processing speed, general executive function, perceptual reasoning, verbal comprehension, reading, and math. Given that the DNA-methylation measures we examined were originally developed in adults, our results suggest that social inequalities may produce in children molecular signatures that, when observed in adults, are associated with chronic inflammation, advanced aging, and reduced cognitive function. Salivary DNA-methylation profiles might be useful as a surrogate endpoint in assessing the effectiveness of psychological and economic interventions that aim to reduce negative effects of childhood social inequality on lifespan development.

Keywords: DNA-methylation; epigenetics; cognition; children; socioeconomic status; racism

Introduction

Children's cognitive function and educational performance are sensitive to environmental input, robustly predict their future social attainments and health (1), and consistently differ by major dimensions of social inequality, such as parental education, income, and race (2, 3). Socioeconomic and racial disparities in child cognitive development arise through various factors tied to classism and racism, including inequitable access to high-quality childcare, educational resources, healthcare, nutrition, and differences in exposure to toxicants, family stress, and neighborhood threat, among other factors (4, 5). For example, the social advantage of White identity, or White privilege, describes the generational legacy of social power experienced by White people through state-sanctioned social marginalization, which persistently shapes the disadvantaged context that young Black and Latinx youth face in the US. Due to the chronic nature of interpersonal and vicarious discrimination in their day-to day lives, indicators of socioeconomic disadvantage capture relevant but limited aspects of the effects of racism on child development (6).

Epigenetic mechanisms that regulate the expression of genes are hypothesized to be involved in the biological embedding of environmental privilege and disadvantage (7). For instance, a consistent finding from experimental manipulations of the social environment in nonhuman animals is that social adversity increases expression of genes linked to inflammation (8), which can modulate the continued development and function of the brain (7). Thus, epigenetic mechanisms actuated by classism and racism may, in part, contribute to social disparities in children's cognitive function.

New advances of genome-wide technology and "omic" approaches have now quantified molecular signatures of a host of exposures, biological processes, and phenotypes that can be used to investigate the etiology of social disparities in life course development. For example, studies have identified patterns of DNA methylation across the epigenome in association with a peripheral proxy for systemic inflammation (9), multisystem biological aging processes (10), and psychological phenotypes (11). Results from such *discovery* studies can be used in *prediction* studies to construct epigenetic profiles in new samples that can then be examined in relation to a wide range of measured variables.

DNA-methylation discovery studies most commonly analyze methylation from blood or other tissues, but not methylation in salivary DNA, which comes from a mixture of buccal cells and leukocytes (https://ngdc.cncb.ac.cn/ewas/statistics). DNA methylation is a dynamic process and can be tissue-specific with, for example, different epigenetic signatures in brain, blood, and saliva (12). Yet, because DNA-methylation profiling using saliva is amenable at large scale in pediatric samples, this method offers distinct opportunities for large-scale epidemiological and longitudinal studies. Specifically, salivary DNA-methylation profiles may be useful for examining the etiology of social disparities in lifespan development. However, little work has been conducted to-date to examine whether salivary DNA-methylation measures are sensitive to social inequality (though see (13)) and associated with psychological development in children and adolescents.

Following preregistered analyses (https://osf.io/x978n/), we examined whether salivary DNA-methylation measures derived from discovery studies trained on inflammation, cognitive function, and the pace of biological aging are (a) stratified by major dimensions of social inequality and (b) associated with cognitive functions in children and adolescents. Three salivary DNA-methylation composite scores were of particular interest in the present study, because their blood-derived composites have been associated with cognitive function or they have been found to be sensitive to socioeconomic inequality. First, we examined DNA-methylation profiles of C-reactive protein (CRP; "DNAm-CRP"), which in blood samples have previously been found to be associated with cognitive functions in adults (14) and children (15). Second, we examined "Epigenetic-g" from a blood-based epigenome wide association study of general cognitive functions (g) in adults, which accounted for 3.4% and 4.5% of the variance in general cognitive functioning in two external adult cohorts using methylation from blood samples (11). Third, we examined "DunedinPoAm", which was developed from analysis of rate of longitudinal change in organ system integrity occurring in middle-adulthood in a cohort of individuals who were all the same chronological age (16). We previously reported that socioeconomic disadvantage and Latinx compared to White identity is associated with faster pace of biological aging, as indicated by the DunedinPoAm, in a previous data freeze of Texas Twins salivary DNA-methylation data (N=600; (13)). In contrast, epigenetic clocks and the mortality predictor "GrimAge" were not sensitive to socioeconomic inequality and therefore not considered in analyses reported here (DNAm-CRP and Epigenetic-g were not previously examined). In the present study, we also examined whether genetic profiles of inflammation (*i.e.* polygenic scores of CRP, (17)) are associated with cognitive functions. Participants were 1183 (609 female) children and adolescents with at least one DNA-methylation sample from the population-representative Texas Twin Project, including 426 monozygotic and 757 dizygotic twins from 611 unique families, aged 8 to 19 years (mean age = 13.38 y, *SD* = 2.99 y).

Results

The preregistration of our analysis plan can be found at https://osf.io/krgfs/.

Salivary DNA-methylation profiles in children are reliably measured and show expected patterns of association with covariates

DNA-methylation profiles (*i.e.,* DNAm-CRP, Epigenetic-g, DunedinPoAm) measured from salivary DNA were approximately normally distributed (see **Table 1** for descriptive statistics before correction for the cell composition of saliva samples). Analyses of 15 technical replicates suggested moderate-to-good reliability of DNA-methylation profiles residualized for technical artifacts and cell composition (ICC for DNAm-CRP = 0.73, epigenetic-g = 0.80, DunedinPoAm = 0.84). Biometric models using the twin family structure, where the similarity between twins due to both additive genetic factors (*A*) and environmental factors shared by twins living in the same home (*C*) represents a lower bound estimate of reliability, also suggested good reliability of

DNA-methylation profiles ($A+C$ variation for DNAm-CRP= 60.7%, Epigenetic-g = 55.3%, DunedinPoAm = 54.2%, accounting for age and gender).

Higher DNAm-CRP was strongly correlated with higher DunedinPoAm (r=0.89 [95% CI= 0.81, 0.96], p<0.001, accounting for age and gender) and moderately correlated with lower Epigenetic-g (r=-0.31 [-0.42, -0.19], p<0.001). This result is unsurprising as CRP levels were one of the 18 biomarkers that the DunedinPoAm measure was trained on (16). Lower Epigenetic-g was weakly correlated with higher DunedinPoAm (r=-0.17 [-0.29, -0.04], p=0.011).

Older children had higher DNAm-CRP (r =0.35 [0.26, 0.44], p<0.001), Epigenetic-g (r=0.64 [0.56, 0.72], p<0.001), and DunedinPoAm profiles (r=0.13 [0.02, 0.23], p=0.018). Boys had lower DNAm-CRP (d =-0.26 [-0.34, -0.18], p<0.001) and DunedinPoAm (d =-0.18 [-0.27 - 0.10], p<0.001), but not Epigenetic-g profiles (d =0.06 [-0.02, 0.14], p=0.143). All models included age, gender, and an age by gender interaction as covariates.

Salivary DNA-methylation profiles are socially stratified in children

Salivary DNA-methylation profiles in children were socially stratified. Children from socioeconomically disadvantaged families, socioeconomically disadvantaged neighborhoods, neighborhoods with less intergenerational economic mobility (*i.e.,* neighborhood opportunity), and children reporting Latinx-only or Black+ identity relative to White-only identity exhibited DNA-methylation profiles associated with higher chronic inflammation, a faster pace of biological aging, and lower cognitive functioning (see **Figure 1** and **Supplemental Table S1**). Children reporting Black+ and Latinx-only identities lived in the most socioeconomically disadvantaged families and neighborhoods compared to children reporting White-only identity (see **Figure 2** and **Supplemental Table S2**). Family-level socioeconomic disadvantage accounted for racial/ethnic disparities in DNAm-CRP, but not Epigenetic-g. Family-level socioeconomic disadvantage accounted for the difference in DunedinPoAm between Black+, but not Latinx-only, relative to White-only identity (see **Supplemental Table S1)**. See **Supplemental Table S3** for effect size estimates between socioeconomic inequality and DNA-methylation profiles reported separately for each racial/ethnic group (this analysis was not preregistered).

Comparing White-only identifying children to all other groups (this comparison was not preregistered) indicated that the advantage, or privilege, of White identity compared to other racial/ethnic categories was evident in all three DNA-methylation profiles (DNAm-CRP r = -0.14 [-0.22, -0.06], p<0.001; Epigenetic-g r= 0.23 [0.16, 0.31], p< 0.001; DunedinPoAm r=-0.25 [-0.34, -0.16], p<0.001). White identity remained evident in Epigenetic-g (r=0.21 [0.13, 0.29], p<0.001) and DunedinPoAm (r=-0.19 [-0.29, -0.09], p<0.001), but not DNAm-CRP (r=-0.08 [-0.17, 0.01], p=0.067), after accounting for the lower rates of family-level disadvantage experienced by White children (r=-0.29 [-0.38, -0.19], p<0.001). Effects of White identity were reduced but also still remained evident in Epigenetic-g (r=0.17 [0.09– 0.25], p<0.001) and DunedinPoAm (r =-0.16, [-0.26, -0.05], p=0.003), but not DNAm-CRP (r=-0.04 [-0.13, 0.05], p=0.373), after accounting for both the lower rates of family-level (r=-0.30 [-0.39, -0.21],

$p<0.001$) and neighborhood-level socioeconomic disadvantage (r=-0.34 [-0.42, -0.26], $p<0.001$) experienced by White children.

We next examined the role of body mass index (BMI), pubertal stage, and DNA-methylation profiles related to smoking (DNAm-smoke) in associations of social inequality and DNA-methylation profiles of interest. Socioeconomic and racial/ethnic inequalities in DNA-methylation largely remained after including these covariates, with the exception that correlations with DNAm-CRP were largely accounted for by including BMI (see **Supplemental Table S1**).
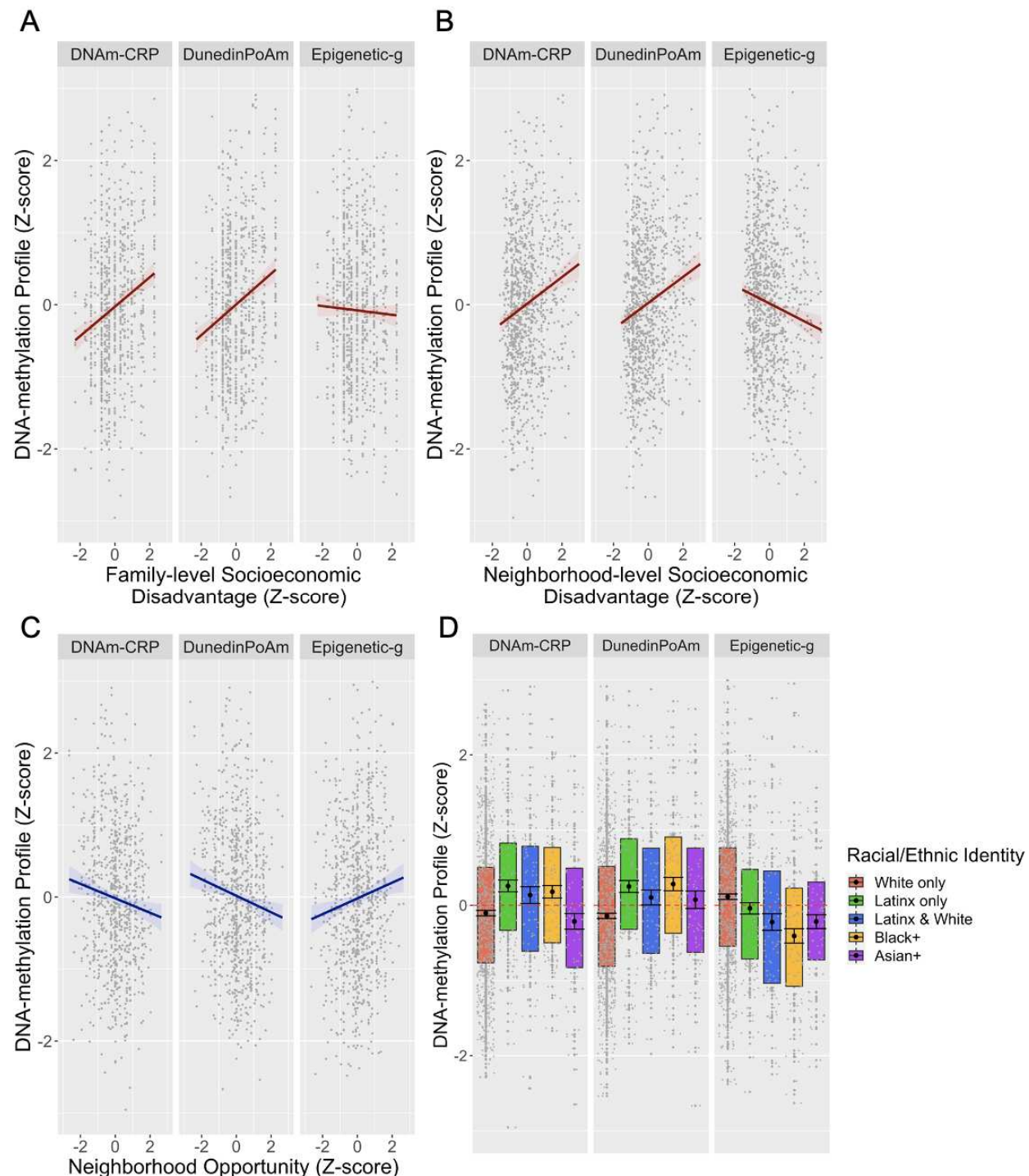
Figure 1. **Associations between A) family-level socioeconomic disadvantage, B) neighborhood-level socioeconomic disadvantage, C) neighborhood opportunity (*i.e.,* intergenerational economic mobility), and D) self-identified racial/ethnic identity with three DNA-methylation profiles (DNAm-CRP, DunedinPoAm, and Epigenetic-g) in children and adolescents.** DNA-methylation profiles and socioeconomic disadvantage values are in standard deviation units. Higher DNAm-CRP values indicate a methylation profile associated with higher chronic inflammation. Higher DunedinPoAm values indicate a methylation profile associated

with faster biological aging. Higher Epigenetic-g values indicate a methylation profile associated with higher cognitive functioning. The racial/ethnic identity boxplots display group DNA-methylation differences in the mean (black circle), standard errors of the mean (error bars), the first and third quartiles (lower and upper hinges), and the mean across groups (red dashed line). Participants self-identified as White only (62%), Latinx only (12.2%), Latinx and White (8.1%), Black and potentially another race/ethnicity (10%), Asian and potentially another race/ethnicity but not Latinx or Black (7.5%), and Indigenous American, Pacific Islander or other, but not Latinx, Black, or Asian (0.6%, not shown due to small sample size). See **Supplemental Table S1** for standardized regression coefficients with and without covariate controls for body mass index, puberty, and socioeconomic inequality.
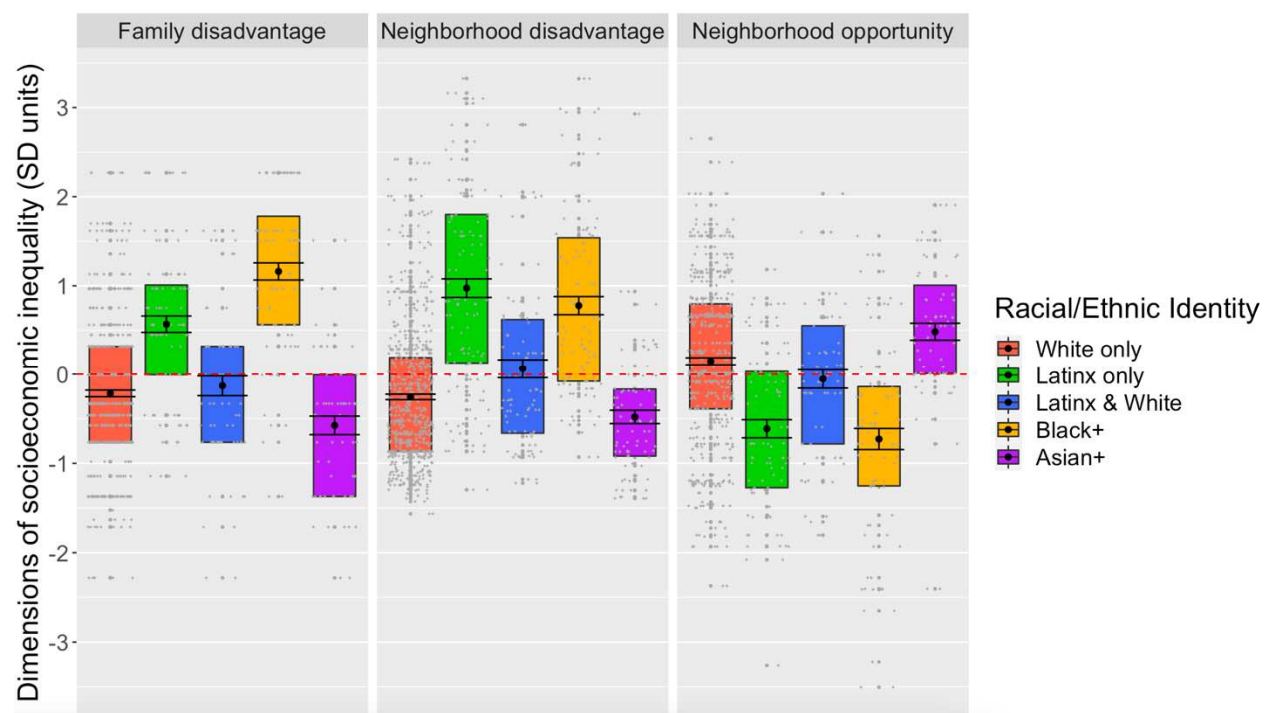

Figure 2. **Associations between racial/ethnic identity and dimensions of socioeconomic inequality.** Socioeconomic disadvantage and opportunity values are Z-scores. The racial/ethnic identity boxplots display group DNA-methylation differences in the mean (black circle), standard errors of the mean (error bars), the first and third quartiles (lower and upper hinges), and the mean across groups (red dashed line). Participants self-identified as White only (62%), Latinx only (12.2%), Latinx and White (8.1%), Black and potentially another race/ethnicity (10%), Asian and potentially another race/ethnicity but not Latinx or Black (7.5%), and Indigenous American, Pacific Islander or other, but not Latinx, Black, or Asian (0.6%, not shown due to small sample size). See **Supplemental Table S2** for standardized regression coefficients.

Salivary DNA-methylation profiles are associated with cognitive functions

Salivary DNA-methylation profiles were associated with performance on multiple in-laboratory tests of cognitive functioning: Higher DNAm-CRP was associated with worse performance on tests of processing speed, general executive function, perceptual reasoning, and

verbal comprehension. Lower Epigenetic-g was associated with lower scores on tests of perceptual reasoning, verbal comprehension, reading, and math. Finally, faster pace of biological aging was associated with lower scores on tests of verbal comprehension and perceptual reasoning (see **Figure 3** and **Supplemental Table S4**). Notably, the largest effect size was observed for Epigenetic-g and math, where Epigenetic-g explained R^2=11.1% of the variation in math performance. See **Supplemental Table S5** for effect size estimates between DNA-methylation profiles and cognition reported separately for each racial/ethnic group (this analysis was not preregistered).

As all three DNA-methylation profiles were associated with perceptual reasoning and verbal comprehension, we performed commonality analyses to examine the proportion of overlapping and unique variation explained. DNAm-CRP and DunedinPoAm explained largely overlapping variation in perceptual reasoning (DNAm-CRP alone: 2.6%, DunedinPoAm alone: 4%, combined: 3.8%) and verbal comprehension (DNAm-CRP alone: 2%, DunedinPoAm alone: 3.4%, combined: 3.8%). Whereas Epigenetic-g explained unique variation in perceptual reasoning (Epigenetic-g alone: 2.4%) and verbal comprehension (Epigenetic-g alone: 2.9%) relative to both DNAm-CRP (perceptual reasoning combined: 5.9%, verbal comprehension combined: 5.5%) and DunedinPoAm (perceptual reasoning combined: 6.5%, verbal comprehension combined: 6.3%).

We next examined the role of BMI, puberty, DNAm-smoke, and family-level disadvantage in associations of DNA-methylation measures with cognitive test performance. Associations were largely unaffected by controlling for BMI, puberty, and DNAm-smoke, with the exception that associations of DNAm-CRP with cognition were mostly accounted for by controlling for BMI. Associations of DNAm-CRP and DunedinPoAm with cognition were largely accounted for by controlling for family-level disadvantage, with the exception of perceptual reasoning. In contrast, associations of Epigenetic-g with cognitive test performance were unaffected by controlling for family-level disadvantage (**Supplemental Table S4**).

We assessed potential effects of differing sample sizes of cognitive measures (**Table 1**) on effect size estimates (this analysis was not preregistered). Effect size estimates based on models using listwise deletion were largely similar to reported results, suggesting that differing sample sizes across measures did not substantially affect effect sizes (see **Supplemental Figure 1**).

We further examined the extent to which DNA-methylation associations with cognition are robust to complete genetic and family-level environmental control in a bivariate biometric model that used the twin family structure of the Texas Twin Project. Consistent with the hypothesis that DNA-methylation associations with cognitive function represents (partially unmeasured) effects of family-level stratification, we found no evidence to suggest that identical twins who differ from their co-twins in DNA-methylation show corresponding differences in their cognitive functioning (see **Supplemental Table S6**).

Genetic profiles of CRP are not associated with cognitive functions

PGS-CRP analyses were restricted to participants who had European genetic ancestries as indicated by principal components of genetic ancestry that were comparable to the GWAS discovery sample. PGS-CRP were not associated with measures of cognitive functioning (see **Figure 1** and **Supplemental Table S4**). PGS-CRP did not account for differences in cognitive function between dizygotic twins (see **Supplemental Figure S1**). Because of the sample size of dizygotic twin pairs (N=364) we preregistered the previous analysis as primarily exploratory.
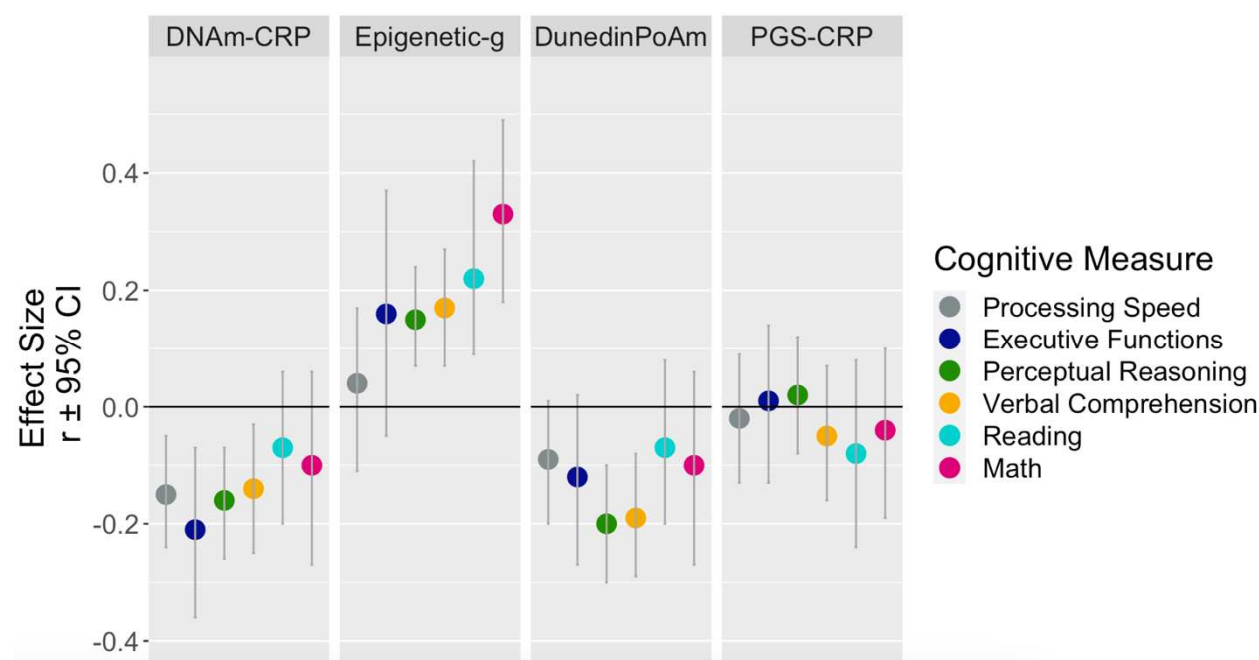

Figure 3. **Associations between three DNA-methylation profiles (DNAm-CRP, Epigenetic-g, and DunedinPoAm) and a polygenic score of inflammation (PGS-CRP) with six measures of cognitive functioning in children and adolescents.** The plot depicts the standardized regression coefficients (*r*) and 95% confidence intervals (CIs) calculated by regressing cognitive functions on DNA-methylation measures and PGS-CRP, separately. PGS analyses were restricted to participants solely of recent European ancestries as indicated by genetic ancestry PCs that are comparable to the GWAS discovery sample. All models included covariate adjustment for child's age and gender, and technical covariates. Higher cognitive values indicate higher task performance. Higher DNAm-CRP and PGS-CRP values indicate a methylation profile and genetic profile of higher chronic inflammation, respectively. Higher Epigenetic-g values indicate a methylation profile associated with higher cognitive functioning. Higher DunedinPoAm values indicate a methylation profile of faster biological aging. See **Supplemental Table S4** for standardized regression coefficients with and without covariate controls for body mass index, puberty, and socioeconomic inequality.

Discussion

We analyzed salivary DNA-methylation data from 1183 children and adolescents participating in the Texas Twin Project to examine whether salivary DNA-methylation measures of inflammation, cognitive function, and the pace of aging are (a) stratified by major dimensions of social inequality and (b) associated with performance on test of cognitive functions in childhood. We found that children and adolescents growing up in more socioeconomically disadvantaged families and neighborhoods and children from marginalized racial/ethnic groups compared to their more privileged peers exhibit DNA-methylation profiles associated with higher chronic inflammation, lower cognitive functioning, and a faster pace of biological aging. Moreover, these socially stratified DNA-methylation profiles were related to scores on multiple in-laboratory cognitive tests, including tests of processing speed, general executive function, perceptual reasoning, verbal comprehension, reading, and math. Associations of DNA-methylation measures of inflammation and the pace of aging with cognition were largely accounted for by controlling for family-level socioeconomic disadvantage.

Given that the DNA-methylation measures we examined were originally developed in adults, our results suggest that social inequalities may produce in children molecular signatures that, when observed in adults, are associated with chronic inflammation, advanced aging, and reduced cognitive function. Our findings indicate that salivary DNA-methylation measures, originally validated in adult blood samples, may be useful for indexing social inequality and risk for disparities in cognitive function in childhood and adolescence, sensitive developmental periods in which cognitive functions are susceptible to environmental inputs. Our cross-sectional, observational design did not allow us to examine whether policy changes mitigating socioeconomic inequality (*e.g.,* increases in minimum wage, child tax credits) and structural racism (*e.g.,* eliminating the legacy of redlining, police reforms) affects children's DNA-methylation profiles. Such investigations remain high-priority areas for future research. Salivary DNA-methylation measures may be useful as surrogate endpoints for assessing the effectiveness of programs and policies that aim to reduce effects of childhood social inequality on lifespan development.

Our analysis of racial/ethnic group differences found that children reporting Latinx-only or Black+ relative to White-only social identity exhibited higher chronic inflammation, faster pace of biological aging, and lower cognitive functioning, as indicated by DNA-methylation measures. Children reporting Black+ or Latinx-only identity lived, on average, in substantially more socioeconomically disadvantaged families and neighborhoods compared to children reporting White-only identity. Socioeconomic disadvantage statistically accounted for some, but not all, of the differences between racial/ethnic groups in DNA-methylation profiles. For example, the social advantage of White identity, or White privilege, remained evident in DNA-methylation profiles after accounting for the lower rates of both family-level and neighborhood-level disadvantage experienced by White families. Thus, our findings are consistent with observations that racial and ethnic disparities leave biological traces in the first two decades of life and reflect multiple dimensions of social inequality (4, 5). Family and neighborhood

indicators of socioeconomic disadvantage, privilege, and intergenerational mobility capture relevant but limited aspects of the effects of racism on child development (6). Additional factors that are often neglected, such as the impact of race-based discrimination in education and healthcare systems and chronic exposure to interpersonal and vicarious discrimination in daily life, may explain further variance in the effects of racial/ethnic marginalization (18–20). Given that research in developmental psychology investigating the role of race, including racial disparities in adversity, is rare, scientific understanding of how racism manifests in children's lives and affects their development remains limited (21).

We found that salivary DNA-methylation profiles were associated with several measures of cognitive functioning with non-negligible effect sizes. After correcting for multiple comparisons, DNA-methylation profiles of higher inflammation were associated with lower in-laboratory processing speed, general executive function, perceptual reasoning, and verbal comprehension. Lower Epigenetic-g was associated with lower perceptual reasoning, verbal comprehension, reading, and math performance. Faster pace of biological aging was correlated with lower verbal comprehension and perceptual reasoning. Notably, Epigenetic-g explained 11.1% of the variation in math performance.

DNA methylation is a dynamic process and can be tissue specific with, for example, different epigenetic signatures in brain, blood, and saliva. Whereas we measured methylation in salivary DNA, the original estimates on which our profiles were based were estimated from DNA methylation in blood. Recent research suggests that salivary DNA-methylation collected with Oragene kits (as was done here) in children is particularly enriched for immune cells rather than epithelial cells (22). It may therefore be particularly sensitive to inflammatory processes, which contribute to DNA-methylation profiles of inflammation (DNAm-CRP) and pace of aging (DunedinPoAm). In contrast, genetic profiles related to inflammation (*i.e.,* polygenic scores of CRP) were not associated with cognitive functioning. Our findings linking DNAm-CRP with DunedinPoAm and cognitive functioning are in line with experimental animal studies reporting that social adversity increases expression of genes linked to inflammation, which may be critically involved in multi-system aging processes (*i.e.*, "inflammaging") and can modulate the development of the brain (7, 8). Yet, the measurements we studied are molecular derivatives of unobserved inflammatory processes, not direct observations of chronic inflammation. Accordingly, this type of omics research is not well-suited to identifying precise biological processes.

In conclusion, our findings suggest that salivary DNA-methylation profiles are promising candidate biomarkers of major dimensions of social inequality experienced in real-time during childhood. Because saliva can easily be collected in large-scale pediatric epidemiological studies, salivary DNA-methylation profiles might be useful as surrogate endpoints in evaluation of ontogenetic theories and social programs that address the childhood social determinants of lifelong cognitive disparities.

Method

Sample

The Texas Twins Project. The Texas Twin Project is an ongoing longitudinal study that includes the collection of saliva samples for DNA and DNA-methylation extraction since 2012 (23). Participants in the current study were 1213 (622 female) children and adolescents, including 433 monozygotic and 780 dizygotic twins (see zygosity measure) from 617 unique families, aged 8 to 19 years ($M = 13.66$, $SD = 3.06$) that had at least one DNA-methylation sample. 195 participants contributed two DNA-methylation samples (time between repeated samples: $M = 22$ months, $SD = 6.5$, range $3 - 38$ months) and 16 samples were assayed in duplicate for reliability analyses (total methylation sample n = 1424). Participants self-identified as White only (62%), Latinx only (12.2%), Latinx and White (8.1%), Black and potentially another race/ethnicity (10%), Asian and potentially another race/ethnicity but not Latinx or Black (7.5%), and Indigenous American, Pacific Islander or other, but not Latinx, Black, or Asian (0.6%). The University of Texas Institutional Review board granted ethical approval. Please see **Table 1** for descriptive statistics**,** including sample sizes for each measure after exclusion based on DNA-methylation preprocessing.

Measures

DNA-methylation

DNA-methylation preprocessing. Saliva samples were collected during a laboratory visit using Oragene kits (DNA Genotek, Ottawa, ON, Canada). DNA extraction and methylation profiling was conducted by Edinburgh Clinical Research Facility (UK). The Infinium MethylationEPIC BeadChip kit (Illumina, Inc., San Diego, CA) was used to assess methylation levels at 850,000 methylation sites. DNA methylation preprocessing was primarily conducted with the 'minfi' package in R (24). Within-array normalization was performed to address array background correction, red/green dye bias, and probe type I/II correction, and it has been noted that at least part of the probe type bias is a combination of the first two factors (Dedeurwaerder et al., 2014). Noob preprocessing as implemented by minfi's "preprocessNoob" (25) is a background correction and dye-bias equalization method that has similar within-array normalization effects on the data as probe type correction methods such as BMIQ (Teschendorff et al., 2013).

In line with our preregistered preprocessing plan, CpG probes with detection p > 0.01 and fewer than 3 beads in more than 1% of the samples and probes in cross-reactive regions were excluded (26). None of these failed probes overlapped with the probes used for DNA-methylation scores. 44 samples were excluded because (1) they showed low intensity probes as indicated by the log of average methylation <9 and their detection p was > 0.01 in >10% of their probes, (2) their self-reported and methylation-estimated sex mismatch, and/or (3) their self-reported and DNA-estimated sex mismatch. Cell composition of immune and epithelial cell types (*i.e.,* CD4+ T-cell, natural killer cells, neutrophils, eosinophils, B cells, monocytes, CD8+ T-cell, and granulocytes) were estimated using a newly developed child saliva reference panel implemented in the R package "BeadSorted.Saliva.EPIC" within "ewastools" (22). Surrogate

variable analysis was used to correct methylation values for batch effects using the "combat" function in the SVA package (27).

DNA-methylation scores.

DNAm-CRP. DNAm-CRP was computed on the basis of an epigenome-wide association study of CRP (9). Using the summary statistics of the associations between CpG sites and adult CRP, we created one methylation score per person by summing the product of the weight and the individual beta estimate for each individual at each of the 218 CpG sites significantly associated ($p < 1.15 \times 10^{-7}$) with CRP.

DunedinPoAm. DunedinPoAm was developed from DNA-methylation analysis of Pace of Aging in the Dunedin Study birth cohort. Pace of Aging is a composite phenotype derived from analysis of longitudinal change in 18 biomarkers of organ-system integrity measured when Dunedin Study members were all 26, 32, and 38 years of age (28). Elastic-net regression machine learning analysis was used to fit Pace of Aging to Illumina 450k DNA-methylation data generated from blood samples collected when participants were aged 38 years. The elastic net regression produced a 46-CpG algorithm. Increments of DunedinPoAm correspond to "years" of physiological change occurring per 12-months of chronological time. The Dunedin Study mean was 1, *i.e.* the typical pace of aging among 38-year-olds in that birth cohort. Thus, 0.01 increment of DunedinPoAm corresponds to a percentage point increase or decrease in an individual's pace of aging relative to the Dunedin birth cohort at midlife. DunedinPoAm was calculated based on the published algorithm (16) using code available at https://github.com/danbelsky/DunedinPoAm38.

Epigenetic-g. Salivary "epigenetic-g" was computed on the basis of a blood-based epigenome wide association study of general cognitive functions (*g*) in adults (11). We calculated epigenetic-g based on the algorithm available at https://gitlab.com/danielmccartney/ewas_of_cognitive_function. Prior to computation, methylation values were scaled within each CpG site (mean = 0, SD = 1). All DNA-methylation scores were residualized for array, slide, batch, cell composition and then standardized to ease interpretation.

Genetics

Genotyping and imputation. DNA samples were genotyped at the University of Edinburgh using the Illumina Infinium PsychArray, which assays ~590,000 single nucleotide polymorphisms (SNPs), insertions-deletions (indels), copy number variants (CNVs), structural variants, and germline variants across the genome. Genetic data was subjected to quality control procedures recommended for chip-based genomic data (29, 30). Briefly, samples were excluded on the basis of poor call rate (< 98%) or inconsistent self-reported and biological sex, while variants were excluded if missingness exceeded 2%. As further variant-level filtering has been shown to have a

detrimental effect on imputation quality (31), quality control thresholds for minor allele frequency (MAF) and Hardy–Weinberg equilibrium (HWE) were applied after phasing and imputation.

Untyped markers were imputed on the Michigan Imputation Server (https://imputationserver.sph.umich.edu). Specifically, genotypes were phased and imputed with Eagle v2.4 and Minimac4 (v1.5.7), respectively, while using the 1000 Genomes Phase 3 v5 reference panel (32). To ensure that only high-quality typed and imputed markers were used for analysis, variants were excluded if they had a MAF < 1e-3, a HWE p-value < 1e-6, or an imputation quality score < .90. These procedures produced a final set of 4,703,309 genetic markers to be used in analyses.

DNA preprocessing. DNA samples were genotyped at the University of Edinburgh using the Illumina Infinium PsychArray, which assays ~590,000 single nucleotide polymorphisms (SNPs), insertions- deletions (indels), copy number variants (CNVs), structural variants, and germline variants across the genome. Genotypes will be subjected to quality control procedures recommended for chip-based genomic data (29, 30). Briefly, samples will be excluded due to poor call rate (< 98%) and inconsistent self-reported and biological sex. Variants will be excluded if more than 2% of data is missing. Untyped variants will be imputed on the Michigan Imputation Server (https://imputationserver.sph.umich.edu). As part of this process, genotypes will be phased with Eagle v2.4 and imputed with Minimac4 (v1.5.7), using the 1K Genomes Phase 3 v5 panel as a reference panel (32). Thresholds for minor allele frequency (MAF < 1e-3) and Hardy-Weinberg Equilibrium (HWE p-value < 1e-6) will be applied after phasing and imputation, as variant-level filtering has been shown to have a detrimental effect on imputation quality (31). Finally, imputed genotypes will be excluded if they suffer from poor imputation quality (INFO score < .90).

Polygenic scores. PGS-CRP was computed in two steps. First, GWAS summary statistics were adjusted for linkage disequilibrium, or LD (i.e., correlation structures in the genome that capture population stratification). The preregistered analysis plan proposed using SBayesR (33) for LD-adjustment. However, as the GWAS summary statistics used to compute PGS-CRP did not meet the data requirements of SBayesR (e.g., effect allele frequency, per SNP sample size), we elected to use PRScs for LD-adjustment instead. PRScs is a program that uses Bayesian regression to infer posterior SNP effects using continuous shrinkage priors. PRScs has been shown to improve prediction accuracy of PGSs over other widely used PGS approaches (34). PRScs requires GWAS summary statistics and an external reference panel of the same ancestry as the GWAS. For the summary statistics, we used publicly available data from a GWAS of CRP in 204,402 individuals solely of European ancestry (17). For the reference panel, we used the 1000 Genomes Project (32) European reference panel (phase 3 v5; provided with the software) that was restricted to HapMap3 SNPs (35).

Second, we used PLINK v2 (36) to apply the LD-adjusted SNP effects from PRScs in the Texas Twins Project sample. The resulting PGS-CRP is described by the following equation:

$$PGS = \sum_{i}^{m} x_i \widehat{\beta}_i$$

where m is the number of SNPs, $\hat{\beta}$ is the estimated effect of the ith SNP and x, coded as 0, 1 or 2, is the number of effect alleles of the ith SNP. All PGS analyses were restricted to individuals solely of European ancestries in order to reduce the risk of spurious findings due to population stratification. PGS-CRP was residualized for the top five genetic principal components and genotyping batch and then standardized using Z-scores (M=1; SD=0).

Cognitive function
Processing speed. Three tasks were used to construct a latent measure of processing speed that were available in participants in grades three through eight: Symbol Search (Wechsler, 2003) Pattern Comparison, and Letter Comparison (Salthouse & Babcock, 1991). Each task assessed how quickly and accurately participants identified similarities between symbols, patterns, or letters.

Executive functions. The current study included 15 tasks assessing 4 EF domains that were available in participants in grades three through eight: inhibition, switching, working memory, and updating. Tasks were administered orally, on the computer, or on paper. Inhibition was assessed with four tasks: Animal Stroop (39), Mickey (40), and Stop Signal. The study originally used an auditory Stop Signal task (41), which was replaced with a visual Stop Signal task (42) after the third year of data collection to accommodate the needs of administering EF tasks in the MRI scanner. Switching was assessed using four tasks: Trail Making (Salthouse, 2011), Local-Global (44), Plus-Minus (44), and a computerized Cognitive Flexibility task (45). Cognitive Flexibility replaced the Plus-Minus task, again to accommodate MRI task administration after the third year of data collection. Working memory was assessed using three tasks: Symmetry Span (46), Digit Span Backward (37), and Listening Recall (47). These tasks tap spatial, verbal, and auditory working memory, respectively. Updating was assessed with four tasks: Keeping Track (44), Running Memory for Letters (48), 2-Back task (49), and, as a replacement to the 2-Back task after the third year of data collection, a 1- and 2-back task (49). More comprehensive task descriptions can be found in Engelhardt et al. (50).
Previous research in this sample (50, 51) demonstrated that variation in EF is best captured by a hierarchical factor model, with individual EF tasks loading onto one of four latent factors representing each EF domain and each of these loading onto a common EF factor. This same hierarchical model was adopted in all the analyses presented in the current research to examine general EF.

Verbal comprehension and Perceptual reasoning

We administered the Wechsler Abbreviated Scale of Intelligence (WASI-II; Wechsler, 2011) to all participants to assess perceptual reasoning, also called non-verbal fluid intelligence, and verbal comprehension, also called verbal crystallized intelligence. Perceptual reasoning is the sum of the age-normed t-scores on the Block Design and Matrix Reasoning subtests. Verbal comprehension is the sum of the age-normed t-scores on the Vocabulary and Similarities subtests.

Math and reading. To assess more specific reading comprehension and mathematics skills, participants in grades three through eight completed the Passage Comprehension and Calculation subtests, respectively, of the Woodcock-Johnson III Tests of Academic Achievement (53). The dependent variable for the reading and math subtests is total number of items correct.

Socioeconomic context.
Family-level socioeconomic disadvantage. The family-level measure was computed from parent reports of household income, parental education, occupation, history of financial problems, food insecurity (based on the US Household Food Security Survey Module (54)), father absence, residential instability (changes in home address), and family receipt of public assistance. These were aggregated to form a composite measure of household-level cumulative socioeconomic disadvantage described in (2), and coded such that higher scores reflect greater disadvantage.

Neighborhood-level socioeconomic disadvantage. The neighbourhood-level measure was composed from tract-level US Census data according to the method described in (2). Briefly, participant addresses were linked to tract-level data from the US Census Bureau American Community Survey averaged over five years (https://www.census.gov/programs-surveys/acs). A composite score of neighbourhood-level socioeconomic disadvantage was computed from tract-level proportions of residents reported as unemployed, living below the federal poverty threshold, having less than 12 years of education, not being employed in a management position, and single mothers. These were aggregated to form a neighbourhood-level socioeconomic disadvantage composite measure described in (2), and coded such that higher scores reflect greater disadvantage.

Neighborhood opportunity.
The neighborhood opportunity measure indexed the intergenerational economic mobility of children of low-income parents. It examines average annual household income in 2014-15 of offspring (born between 1978-1983, who are now in their mid-thirties) of low-income parents (defined as mean pre-tax income at the household level across five years (1994, 1995, 1998-2000) at the 25th percentile of the national income distribution, or $27000/year) within each census tract. Household income was obtained from federal tax return records between 1989-2015, the 2000 and 2010 Decennial Census (US Census Bureau, 2000, 2010; https://data2.nhgis.org/main), and 2005-2015 American Community Surveys

(https://www.census.gov/programs-surveys/acs). Census tracts reflect where the child resided through the age of 23. This data was compiled by and obtained from the Opportunity Atlas (https://opportunityatlas.org; 53) .

Developmental covariates.

Body mass index (BMI). BMI is socially-patterned with high BMI being more common in children from lower socioeconomic status families and neighborhoods (56). BMI is also associated with differential DNA-methylation patterns across the genome (57). We therefore considered BMI in our analysis. We measured BMI from in-laboratory measurements of height and weight transformed to gender- and age-normed z-scores according to the method published by the US Centers for Disease Control and Prevention (https://www.cdc.gov/growthcharts/percentile_data_files.htm).

Pubertal development. Puberty is sometimes reported to onset at younger ages in children growing up in conditions of socioeconomic disadvantage (58). Puberty is also associated with a range of DNA-methylation changes (59, 60). We therefore consider children's pubertal development in our analysis. Pubertal development was measured using children's self-reports on the Pubertal Development Scale (61). The scale assesses the extent of development across five sex-specific domains (for both: height, body hair growth, skin changes; for girls: onset of menses, breast development; for boys: growth in body hair, deepening of voice). A total pubertal status score will be computed as the average response (1 = "Not yet begun" to 4 = "Has finished changing") across all items. Pubertal development was residualized for age, gender, and an age by gender interaction.

Tobacco exposure. Smoking is a socially-patterned health behavior to which children from lower socioeconomic status families and neighborhoods are disproportionately exposed (62). It is also associated with differential DNA-methylation patterns across the genome (63, 64). We therefore considered tobacco exposure in our analysis. We measured tobacco exposure using a DNA-methylation smoking (DNAm-smoke) score created by summing the product of the weight and the individual beta estimate for each individual at each CpG site significantly associated with smoking in the discovery EWAS (63). Excluding self-reported tobacco users (n=53) did not significantly alter results.

Table 1. Descriptive statistics.

Sample	n	M	SD
DNAm-CRP [a]	1365	0.03	0.02
Epigenetic-g [a]	1365	-0.02	0.20
DunedinPoAm [a]	1365	1.02	0.06
PGS-CRP [b]	654	0	1
Processing speed	869	0	1
General executive functions	869	0	1
Perceptual reasoning	1328	104.18	14.48
Verbal comprehension	1329	105.61	14.02
Reading	625	30.97	4.9
Math	619	21.24	6.48
Family-level socioeconomic disadvantage	993	-0.02	0.96
Neighborhood-level socioeconomic disadvantage	1218	-0.02	1
Neighborhood opportunity	950	0.31	0.62
Body mass index	1364	0.4	1.34
Pubertal development	1325	2.61	0.92
Tobacco use (yes/no)	58/631	–	–
DNAm-smoke	1365	-13.62	1.84

[a] After exclusion of participants based on DNA-methylation preprocessing (n=44), excluding technical replicates (n=15), and including repeated samples (n= 182). Means of raw scores before residualizing for cell composition, array, slide, and batch. Scores were standardized (mean = 0, SD = 1) for analyses.
[b] PGS-CRP only computed for individuals solely of recent European ancestries.

Statistical analyses

Six cognitive outcomes were examined in each cognitive model: (1) Processing speed, (2) general executive functions, (3) perceptual reasoning, (4) verbal comprehension, (5) reading, and (6) math.

Regression models. We performed multilevel, multivariate regression models fit with FIML in *Mplus* 8.2 statistical software (65). To account for nesting of repeated measures within individuals, and multiple twin pairs within families, a sandwich correction was applied to the standard errors in all analyses. All models included a random intercept, representing the family-level intercept of the dependent variable, to correct for non-independence of twins. All models included age, gender, and an age by gender interaction as covariates. We controlled for multiple testing using the Benjamini–Hochberg false discovery rate (FDR) method (66).

Declarations

Conflicts of interest: Not applicable.

Ethics approval: The University of Texas at Austin Institutional Review board granted ethical approval.

Consent to participate: Informed consent to participate in the study was obtained from all participants and their parent or legal guardian.

Consent for publication: Not applicable.

Availability of data and material: Because of the high potential for deductive identification in this special population from a geographically circumscribed area, and the sensitive nature of information collected, data from the Texas Twin Project are not shared with individuals outside of the research team.

Code availability: Code will be shared by the first author upon request.

Author Contributions: KPH, EMTD, & LR developed the study concept and design. LR, PT, AS, TM & LV performed the data analysis under the supervision of EMTD and KPH. LR drafted the manuscript. All authors provided critical revisions and approved the final version of the manuscript for submission.

Supplement

Table S1. Associations between socioeconomic inequality and racial/ethnic identity with DNA-methylation profiles.

	DNAm-CRP			Epigenetic-g			DunedinPoAm		
	b	95% CI	*p*	*b*	95% CI	*p*	*b*	95% CI	*p*
No further covariates [a]									
Family-level disadvantage	0.22	0.12– 0.31	**<0.001**	-0.14	-0.23 – -0.04	**0.005**	0.28	0.18– 0.37	**<0.001**
Neighborhood-level disadvantage	0.25	0.17 – 0.33	**<0.001**	-0.23	-0.31– -0.15	**<0.001**	0.24	0.15 – 0.34	**<0.001**
Neighborhood opportunity	-0.12	-0.21– -0.03	**0.012**	0.19	0.10 – 0.28	**<0.001**	-0.19	-0.30 – -0.08	**0.001**
Latinx	0.15	0.07– 0.24	**0.001**	-0.10	-0.17– -0.02	**0.012**	0.18	0.10– 0.27	**<0.001**
Latinx-White	0.10	-0.02– 0.22	0.108	-0.08	-0.17 – 0.01	0.081	0.09	-0.01– 0.19	0.089
Black+	0.08	0.02 – 0.15	**0.012**	-0.30	-0.38– -0.22	**<0.001**	0.19	0.11– 0.28	**<0.001**
Asian+	-0.01	-0.09– 0.07	0.776	-0.10	-0.17– -0.03	**0.004**	0.11	-0.01– 0.22	0.058
Controlling for BMI									
	b	95% CI	*p*	*b*	95% CI	*p*	*b*	95% CI	*p*
BMI	0.33	0.24– 0.42	**<0.001**	-0.13	-0.22– -0.05	**0.001**	0.30	0.21– 0.40	**<0.001**
Family-level disadvantage	0.11	0.01– 0.21	0.024	-0.08	-0.17 – 0.01	0.076	0.19	0.08 – 0.29	**<0.001**
Neighborhood-level disadvantage	0.15	0.07– 0.23	**<0.001**	-0.20	-0.27– -0.12	**<0.001**	0.14	0.05 – 0.24	**0.004**
Neighborhood opportunity	-0.05	-0.15– 0.05	0.314	0.16	0.07 – 0.25	**<0.001**	-0.09	-0.20 – 0.01	0.088
Latinx	0.10	0.01– 0.18	0.029	-0.08	-0.16– -0.01	**0.027**	0.13	0.04– 0.22	**0.004**
Latinx-White	0.07	-0.03– 0.17	0.180	-0.07	-0.15 – 0.02	0.150	0.06	-0.03 – 0.14	0.213
Black+	0.01	-0.07– 0.07	0.975	-0.25	-0.33 – -0.17	**<0.001**	0.11	0.02 – 0.19	**0.011**
Asian+	0.01	-0.07– 0.09	0.857	-0.10	-0.17 – -0.04	**0.003**	0.13	0.02 – 0.24	**0.025**
Controlling for puberty									
	b	95% CI	*p*	*b*	95% CI	*p*	*b*	95% CI	*p*
Puberty	0.13	0.02– 0.24	**0.020**	0.04	-0.05– 0.13	0.392	0.05	-0.07– 0.18	0.402
Family-level disadvantage	0.21	0.12 – 0.31	**<0.001**	-0.12	-0.22– -0.03	**0.011**	0.28	0.18– 0.39	**<0.001**
Neighborhood-level disadvantage	0.25	0.16– 0.34	**<0.001**	-0.23	-0.31 – -0.15	**<0.001**	0.25	0.11– 0.34	**<0.001**
Neighborhood opportunity	-0.12	-0.22 – -0.01	**0.027**	0.20	0.11– 0.30	**<0.001**	-0.17	-0.28– -0.06	**0.003**
Latinx	0.15	0.06– 0.24	**0.001**	-0.10	-0.18– -0.03	**0.008**	0.18	0.09– 0.27	**<0.001**
Latinx-White	0.14	0.01 – 0.26	**0.033**	-0.08	-0.17– 0.01	0.088	0.11	0.01– 0.21	**0.035**
Black+	0.09	0.03 – 0.16	**0.007**	-0.28	-0.36– -0.20	**<0.001**	0.19	0.11– 0.27	**<0.001**
Asian+	-0.01	-0.09 – 0.07	0.801	-0.10	-0.17– -0.03	**0.006**	0.11	-0.01 – 0.22	0.059
Controlling for DNAm-smoke									
	b	95% CI	*p*	*b*	95% CI	*p*	*b*	95% CI	*p*
DNAm-smoke	0.40	0.28– 0.51	**<0.001**	0.34	0.22– 0.45	**<0.001**	0.24	0.11 – 0.37	**<0.001**
Family-level disadvantage	0.21	0.11– 0.30	**<0.001**	-0.11	-0.21 – -0.02	**0.017**	0.28	0.18– 0.38	**<0.001**
Neighborhood-level disadvantage	0.22	0.14– 0.30	**<0.001**	-0.24	-0.31 – -0.16	**<0.001**	0.23	0.14 – 0.33	**<0.001**
Neighborhood opportunity	-0.11	-0.21– -0.02	**0.022**	0.19	0.10– 0.27	**<0.001**	-0.17	-0.27– -0.06	**0.003**
Latinx	0.11	0.03 – 0.20	**0.011**	-0.13	-0.20– -0.05	**0.001**	0.16	0.07– 0.25	**0.001**

	b	95% CI	p	b	95% CI	p	b	95% CI	p
Latinx-White	0.12	0.01 – 0.23	0.048	-0.07	-0.16– 0.01	0.093	0.11	0.01 – 0.20	**0.028**
Black+	0.14	0.07 – 0.20	**<0.001**	-0.23	-0.31– -0.14	**<0.001**	0.22	0.14 – 0.31	**<0.001**
Asian+	-0.02	-0.09 – 0.06	0.677	-0.10	-0.16– -0.03	**0.004**	0.11	-0.01 – 0.22	0.067
	Controlling for family-level disadvantage								
	b	95% CI	p	b	95% CI	p	b	95% CI	p
Family-level disadvantage	0.19	0.07– 0.30	**0.002**	-0.01	-0.11– 0.08	0.764	0.24	0.13 – 0.36	**<0.001**
Latinx	0.10	0.01 – 0.20	0.036	-0.10	-0.17– -0.02	**0.018**	0.12	0.02 – 0.22	**0.019**
Latinx-White	0.12	0.00 – 0.23	0.050	-0.08	-0.17– 0.01	0.081	0.10	0.01 – 0.20	0.047
Black+	0.01	-0.06 – 0.09	0.739	-0.27	-0.35– -0.19	**<0.001**	0.09	-0.01 – 0.18	0.057
Asian+	0.01	-0.08 – 0.09	0.914	-0.10	-0.17– -0.03	**0.005**	0.13	0.02 – 0.24	**0.021**

Standardized regression coefficients (*b*), 95% confidence intervals (CIs), and uncorrected p-values calculated by regressing DNA-methylation measures on socioeconomic measures and racial/ethnic identity with and without controlling for normed BMI z-scores, puberty (residualized for age within each gender), and DNA-methylation profiles of smoking (DNAm-smoke), separately. *P*-values, where FDR corrected *p*-values < 0.05, are marked in bold. [a]All models included covariate adjustment for child's age, gender, and an age by gender interaction. Methylation scores were residualized for technical covariates (array, slide, batch, cell composition).

Table S2. Associations between racial/ethnic identity and dimensions of socioeconomic inequality.

	Family-level disadvantage			Neighborhood-level disadvantage			Neighborhood opportunity		
	b	95% CI	p	b	95% CI	p	b	95% CI	p
Latinx	0.25	0.16 – 0.35	**<0.001**	0.43	0.33– 0.52	**<0.001**	-0.29	-0.41– -0.17	**<0.001**
Latinx-White	0.02	-0.09 – 0.12	0.763	0.04	-0.06– 0.15	0.444	0.03	-0.11– 0.16	0.700
Black+	0.43	0.35 – 0.52	**<0.001**	0.33	0.25– 0.41	**<0.001**	-0.28	-0.38– -0.18	**<0.001**
Asian+	-0.10	-0.19– -0.02	**0.017**	-0.06	-0.13– -0.01	**0.037**	0.09	0.01– 0.17	0.040

Standardized regression coefficients (*b*), 95% confidence intervals (CIs), and uncorrected p-values calculated by regressing socioeconomic measures on racial/ethnic identity. Participants self-identified as White only (62%), Latinx only (12.2%), Latinx-White (8.1%), Black and potentially another race/ethnicity (10%), Asian and potentially another race/ethnicity but not Latinx or Black (7.5%), and Indigenous American, Pacific Islander or other, but not Latinx, Black, or Asian (0.6%, part of reference group due to small sample size). White-only identity is reference group. *P*-values, where FDR corrected *p*-values < 0.05, are marked in bold.

Table S3. Associations between socioeconomic inequality with DNA-methylation profiles for each racial/ethnic group.

	DNAm-CRP			Epigenetic-g			DunedinPoAm		
	b	95% CI	p	b	95% CI	p	b	95% CI	p
White									
Family-level disadvantage	0.11	-0.02–0.24	0.098	0.04	-0.08–0.15	0.505	0.23	0.08–0.37	0.002
Neighborhood-level disadvantage	0.23	0.11–0.35	<0.001	-0.10	-0.21–0.00	0.052	0.21	0.06–0.37	0.007
Neighborhood opportunity	-0.07	-0.19–0.06	0.312	0.14	0.03–0.25	0.013	-0.12	-0.3–0.06	0.182
Latinx									
Family-level disadvantage	0.33	0.07–0.59	0.014	-0.15	-0.31–0.01	0.059	0.118	-0.18–0.42	0.439
Neighborhood-level disadvantage	0.11	-0.12–0.33	0.352	-0.24	-0.43–-0.04	0.019	0.01	-0.27–0.29	0.925
Neighborhood opportunity	-0.18	-0.43–0.07	0.160	0.16	-0.04–0.37	0.111	-0.18	-0.51–0.15	0.278
Latinx-White									
Family-level disadvantage	0.53	0.13–0.93	0.010	-0.17	-0.42–0.09	0.200	0.29	-0.07–0.64	0.118
Neighborhood-level disadvantage	0.19	-0.1–0.47	0.197	-0.31	-0.52–-0.1	0.004	0.11	-0.16–0.38	0.436
Neighborhood opportunity	-0.01	-0.20–0.18	0.945	0.11	-0.08–0.29	0.261	-0.12	-0.33–0.08	0.232
Black +									
Family-level disadvantage	0.06	-0.22–0.34	0.678	-0.24	-0.69–0.21	0.301	0.19	-0.13–0.51	0.252
Neighborhood-level disadvantage	0.49	0.22–0.75	<0.001	-0.25	-0.62–0.15	0.211	0.47	0.14–0.79	0.005
Neighborhood opportunity	-0.24	-0.44–-0.04	0.018	0.13	-0.16–0.42	0.371	-0.25	-0.52–0.02	0.065
Asian +									
Family-level disadvantage	0.08	-0.18–0.34	0.562	-0.05	-0.33–0.23	0.722	0.07	-0.26–0.41	0.668
Neighborhood-level disadvantage	0.07	-0.2–0.33	0.629	-0.13	-0.39–0.14	0.341	-0.10	-0.45–0.25	0.590
Neighborhood opportunity	0.25	-0.36–0.86	0.428	-0.06	-0.64–0.53	0.856	-0.02	-0.85–0.8	0.959

Standardized regression coefficients (*r*) and 95% confidence intervals (CIs) and uncorrected *p*-value calculated by regressing DNA-methylation measures on socioeconomic measures, separately. Participants self-identified as White only (62%), Latinx only (12.2%), Latinx-White (8.1%), Black and potentially another race/ethnicity (10%), Asian and potentially another race/ethnicity but not Latinx or Black (7.5%), and Indigenous American, Pacific Islander or

other, but not Latinx, Black, or Asian (0.6%). All models included covariate adjustment for age, gender, and an age by gender interaction. Methylation scores were residualized for technical covariates (for methylation: array, slide, batch, cell composition).

Table S4. Associations between DNA-methylation and genetic profiles with cognitive functions.

	Processing speed			Executive functions			Perceptual reasoning			Verbal comprehension			Reading			Math		
	r	CI	*p*	*r*	CI	*p*	*r*	CI	*p*	*r*	CI	*p*	*r*	CI	*p*	*r*	CI	*p*
No further covariates [a]																		
DNAm-CRP	-0.15	-0.24 – -0.05	**0.003**	-0.21	-0.36– -0.07	**0.004**	-0.16	-0.26 – -0.07	**0.001**	-0.14	-0.25 – -0.03	**0.013**	-0.07	-0.20 – 0.06	0.310	-0.10	-0.27– 0.06	0.218
Epigenetic-g	0.04	-0.11 – 0.17	0.657	0.16	-0.05– 0.37	0.126	0.15	0.07 – 0.24	**<0.001**	0.17	0.07 – 0.27	**0.001**	0.22	0.09 – 0.42	**0.001**	0.33	0.18 – 0.49	**<0.001**
DunedinPoAm	-0.09	-0.20 – 0.01	0.082	-0.12	-0.27 – 0.02	0.090	-0.20	-0.30 – -0.10	**<0.001**	-0.19	-0.29 – -0.08	**<0.001**	-0.07	-0.20 – 0.08	0.366	-0.10	-0.27 – 0.06	0.218
PGS-CRP	-0.02	-0.13– 0.09	0.738	0.01	-0.13– 0.14	0.957	0.02	-0.08– 0.12	0.690	-0.05	-0.16– 0.07	0.409	-0.08	-0.24– 0.08	0.327	-0.04	-0.19– 0.08	0.553
Controlling for BMI																		
	r	CI	*p*	*r*	CI	*p*	*r*	CI	*p*	*r*	CI	*p*	*r*	CI	*p*	*r*	CI	*p*
BMI	-0.10	-0.18– -0.02	**0.017**	-0.24	-0.35 – -0.12	**<0.001**	-0.18	-0.27 – -0.10	**<0.001**	-0.19	-0.29– -0.08	**0.001**	-0.19	-0.31– -0.06	**0.003**	-0.24	-0.36– -0.12	**<0.001**
DNAm-CRP	-0.09	-0.20 – 0.02	0.115	-0.09	-0.26– 0.07	0.260	-0.10	-0.20 – 0.00	0.053	-0.07	-0.20 – 0.05	0.257	0.03	-0.12– 0.17	0.737	-0.01	-0.17 – 0.15	0.918
Epigenetic-g	-0.01	-0.21 – 0.14	0.956	0.10	-0.12 – 0.32	0.351	0.14	0.06– 0.22	**0.001**	0.15	0.06 – 0.25	**0.001**	0.20	0.06– 0.34	**0.005**	0.30	0.14 – 0.45	**<0.001**
DunedinPoAm	-0.04	-0.16 – 0.08	0.499	-0.02	-0.18– 0.14	0.825	-0.14	-0.25 – -0.04	**0.008**	-0.12	-0.24– -0.01	**0.030**	0.02	-0.13 – 0.17	0.815	0.01	-0.18– 0.19	0.975
PGS-CRP	0.00	-0.11 – 0.10	0.965	0.04	-0.10– 0.17	0.604	0.03	-0.06– 0.12	0.530	-0.04	-0.14– 0.08	0.534	-0.07	-0.22– 0.09	0.388	-0.02	-0.15– 0.12	0.794
Controlling for puberty																		
	r	CI	*p*	*r*	CI	*p*	*r*	CI	*p*	*r*	CI	*p*	*r*	CI	*p*	*r*	CI	*p*
Puberty	-0.12	-0.21– -0.02	**0.019**	-0.14	-0.28 – -0.03	0.043	0.08	-0.03– 0.18	0.159	0.04	-0.09– 0.17	0.547	-0.11	-0.25– 0.03	0.112	-0.07	-0.20– 0.06	0.311
DNAm-CRP	-0.12	-0.22– -0.02	**0.014**	-0.19	-0.34– -0.01	**0.017**	-0.17	-0.26– -0.07	**<0.001**	-0.14	-0.26– -0.03	**0.013**	-0.05	-0.18– 0.09	0.523	-0.11	-0.26– 0.04	0.134
Epigenetic-g	0.03	-0.11– 0.16	0.680	0.16	-0.08– 0.49	0.142	0.15	0.07– 0.23	**<0.001**	0.17	0.07– 0.26	**0.001**	0.22	0.09– 0.36	**0.001**	0.33	0.18– 0.49	**<0.001**
DunedinPoAm	-0.08	-0.18– 0.01	0.125	-0.11	-0.25– 0.04	0.137	-0.20	-0.30– -0.10	**<0.001**	-0.19	-0.29– -0.08	**<0.001**	-0.06	-0.20– 0.09	0.446	-0.10	-0.27– 0.07	0.250
PGS-CRP	-0.01	-0.12– 0.10	0.885	0.02	-0.12– 0.16	0.797	0.01	-0.09– 0.10	0.923	-0.05	-0.16– 0.06	0.386	-0.07	-0.23– 0.09	0.382	-0.04	-0.19– 0.11	0.571
Controlling for DNAm-smoke																		
	r	CI	*p*	*r*	CI	*p*	*r*	CI	*p*	*r*	CI	*p*	*r*	CI	*p*	*r*	CI	*p*
DNAm-smoke	0.08	-0.06– 0.22	0.28	0.08	-0.14– 0.30	0.480	-0.11	-0.22– 0.01	0.081	-0.10	-0.22– 0.03	0.119	-0.17	-0.37– 0.04	0.114	-0.14	-0.37– 0.08	0.205
DNAm-CRP	-0.20	-0.33– -0.07	**0.003**	-0.25	-0.44– -0.06	0.012	-0.13	-0.23– -0.03	**0.011**	-0.12	-0.23– -0.01	0.045	-0.01	-0.16– 0.16	0.972	-0.06	-0.25– 0.13	0.541
Epigenetic-g	0.03	-0.14– 0.20	0.737	0.22	-0.03– 0.48	0.089	0.15	0.07– 0.23	**<0.001**	0.16	0.06– 0.26	**0.002**	0.23	0.09– 0.37	**0.001**	0.35	0.19– 0.50	**<0.001**

	r	CI	p	r	CI	p	r	CI	p	r	CI	p	r	CI	p	r	CI	p
DunedinPoAm	-0.10	-0.22–0.01	0.070	-0.13	-0.28–0.03	0.121	-0.18	-0.28–-0.08	**<0.001**	-0.17	-0.28–-0.07	**0.001**	-0.03	-0.18–0.11	0.646	-0.07	-0.25–0.11	0.46
PGS-CRP	-0.02	-0.13–0.09	0.733	0.00	-0.14–0.14	0.964	0.02	-0.07–0.12	0.665	-0.05	-0.16–0.07	0.416	-0.07	-0.24–0.09	0.368	-0.04	-0.18–0.11	0.636
							Controlling for family-level disadvantage											
	r	CI	p	r	CI	p	r	CI	p	r	CI	p	r	CI	p	r	CI	p
Family-level disadvantage	-0.07	-0.24–0.04	0.170	-0.22	-0.36–-0.08	**0.002**	-0.20	-0.29–-0.11	**<0.001**	-0.29	-0.40–-0.19	**<0.001**	-0.17	-0.31–-0.03	**0.019**	-0.26	-0.41–-0.11	**0.001**
DNAm-CRP	-0.12	-0.39–-0.04	0.013	-0.15	-0.30–-0.01	0.046	-0.11	-0.21–-0.02	**0.020**	-0.07	-0.18–0.05	0.237	-0.04	-0.17–0.10	0.590	-0.08	-0.22–0.07	0.292
Epigenetic-g	0.01	-0.13–0.15	0.877	0.12	-0.10–0.33	0.301	0.15	0.07–0.23	**<0.001**	0.16	0.06–0.25	**0.001**	0.21	0.07–0.35	**0.003**	0.31	0.15–0.47	**<0.001**
DunedinPoAm	-0.07	-0.18–0.04	0.210	-0.06	-0.22–0.09	0.426	-0.15	-0.25–-0.05	**0.004**	-0.11	-0.22–-0.01	0.041	-0.03	-0.1117–0.11	0.673	-0.05	-0.21–0.12	0.564
PGS-CRP	-0.02	-0.13–0.09	0.721	0.00	-0.13–0.14	0.959	0.02	-0.07–0.12	0.675	-0.04	-0.15–0.07	0.444	-0.07	-0.23–0.09	0.376	-0.03	-0.17–0.11	0.645

Standardized regression coefficients (*r*) and 95% confidence intervals (CIs) and uncorrected *p*-value calculated by regressing cognitive functions on DNA-methylation measures and PGS-CRP with and without controlling for normed BMI z-scores, puberty (residualized for age within each sex), DNA-methylation profiles of smoking (DNAm-smoke), and family-level disadvantage separately. *P*-values, where FDR corrected *p*-values < 0.05, are marked in bold. PGS analyses were restricted to participants of European ancestries as indicated by genetic ancestry PCs that are comparable to the GWAS discovery sample. [a]All models included covariate adjustment for age, gender, and an age by gender interaction. Methylation scores and PGS-CRP were residualized for technical covariates (for methylation: array, slide, batch, cell composition; for PGS-CRP: genetic ancestry PCs).

Table S5. Associations between DNA-methylation with cognitive functions for each racial/ethnic group.

	Processing speed			Executive functions			Perceptual reasoning			Verbal comprehension			Reading			Math		
	r	CI	*p*	*r*	CI	*p*	*r*	CI	*p*	*r*	CI	*p*	*r*	CI	*p*	*r*	CI	*p*
White																		
DNAm-CRP	-0.07	-0.19–0.05	0.254	-0.14	-0.33, 0.04	0.134	-0.13	-0.25, -0.02	0.027	-0.01	-0.17, 0.14	0.896	0.08	-0.08, 0.24	0.341	-0.07	-0.25, 0.10	0.421
Epigenetic-g	0.06	-0.16–0.27	0.617	0.11	-0.25, 0.46	0.554	0.12	0.01, 0.23	0.030	0.15	0.01, 0.29	0.038	0.22	0.03, 0.41	0.026	0.40	0.20, 0.60	<0.001
DunedinPoAm	-0.03	-0.20–0.13	0.706	-0.08	-0.30, 0.14	0.466	-0.16	-0.32, 0.00	0.052	-0.04	-0.21, 0.13	0.627	0.09	-0.11, 0.29	0.391	0.024	-0.20, 0.25	0.832
Latinx																		
DNAm-CRP	0.04	-0.22–0.31	0.751	0.07	-0.22, 0.36	0.628	-0.25	-0.53, 0.028	0.078	-0.31	-0.63, 0.02	0.065	-0.22	-0.50, 0.07	0.137	0.11	-0.33, 0.55	0.626
Epigenetic-g	-0.17	-0.66–0.32	0.491	0.01	-0.29, 0.29	0.992	0.05	-0.21, 0.30	0.726	0.25	-0.01, 0.51	0.064	0.18	-0.07, 0.44	0.163	0.07	-0.42, 0.55	0.785
DunedinPoAm	0.18	-0.26–0.62	0.419	0.29	-0.11–0.70	0.156	-0.28	-0.70–0.14	0.193	-0.02	-0.35–0.32	0.920	-0.04	-0.45–0.37	0.843	-0.02	-0.67–0.65	0.965
Latinx-White																		
DNAm-CRP	-0.30	-0.64–0.04	0.079	-0.38	-0.68–-0.09	0.011	-0.03	-0.37–0.31	0.855	-0.09	-0.33–0.14	0.440	-0.26	-0.66–0.14	0.199	-0.27	-0.97–0.43	0.456
Epigenetic-g	0.02	-0.50–0.54	0.933	0.34	-0.01–0.69	0.055	0.35	-0.01–0.70	0.053	0.04	-0.26–0.35	0.789	0.14	-0.38–0.67	0.595	0.53	-0.45–1.51	0.288
DunedinPoAm	-0.20	-0.40–0.01	0.058	-0.14	-0.45–0.17	0.375	-0.23	-0.50–0.04	0.093	-0.28	-0.51–-0.05	0.016	-0.15	-0.44–0.15	0.340	-0.22	-0.80–0.37	0.473
Black+																		
DNAm-CRP	0.00	-0.34–0.35	0.982	-0.01	-0.46–0.44	0.966	-0.13	-0.40–0.13	0.329	-0.24	-0.52–0.04	0.089	0.27	-1.39–1.93	0.749	0.12	-0.94–1.19	0.813
Epigenetic-g	-0.37	-1.18–0.45	0.377	0.05	-0.21–0.30	0.717	0.21	-0.03–0.46	0.092	0.17	-0.06–0.40	0.150	-0.16	-0.95–0.63	0.686	-0.42	-1.12–0.27	0.232
DunedinPoAm	0.01	-0.34–0.35	0.982	0.01	-0.34–0.36	0.962	-0.24	-0.49–0.02	0.066	-0.29	-0.59–0.00	0.051	-0.36	-0.82–0.10	0.13	-0.52	-2.27–1.24	0.564
Asian+																		
DNAm-CRP	0.07	-0.42–0.57	0.771	0.03	-0.35–0.42	0.866	0.17	-0.16–0.51	0.314	0.12	-0.23–0.47	0.511	0.14	-0.31–0.59	0.533	0.05	-0.55–0.64	0.881
Epigenetic-g	0.69	-0.21–1.59	0.131	0.24	-0.38–0.87	0.441	0.12	-0.21–0.46	0.471	0.16	-0.24–0.55	0.438	0.51	-0.05–1.07	0.076	0.88	0.57–1.2	<0.001
DunedinPoAm	0.02	-0.37–0.41	0.935	-0.02	-0.47–0.43	0.922	0.24	-0.10–0.57	0.166	-0.17	-0.53–0.18	0.333	0.08	-0.49–0.65	0.783	0.012	-0.71–0.74	0.973

Standardized regression coefficients (*r*) and 95% confidence intervals (CIs) and uncorrected *p*-value calculated by regressing cognitive functions on DNA-methylation measures, separately. Participants self-identified as White only (62%), Latinx only (12.2%), Latinx-White (8.1%), Black and potentially another race/ethnicity (10%), Asian and potentially another race/ethnicity but not Latinx or Black (7.5%), and Indigenous American, Pacific Islander or other, but not Latinx, Black, or Asian (0.6%). [a]All models included covariate adjustment for age, gender, and an age by gender interaction. Methylation scores were residualized for technical covariates (for methylation: array, slide, batch, cell composition).

Table S6. Co-twin-control associations between DNA-methylation and cognitive functions.

	DNAm-CRP			Epigenetic-g			DunedinPoAm		
	*r*A	CI	*p*	*r*A	CI	*p*	*r*A	CI	*p*
Processing speed	0.12	-0.20– 0.44	0.449	-0.09	-0.58– 0.40	0.723	-0.06	-0.43– 0.32	0.769
Executive functions	-0.10	-0.46– 0.25	0.560	0.04	-0.56– 0.64	0.902	0.21	-0.28– 0.71	0.398
Perceptual reasoning	-0.17	-0.30– -0.04	0.009	0.34	0.07– 0.61	0.014	-0.09	-0.34– 0.16	0.479
Verbal comprehension	0.03	-0.27– 0.32	0.866	0.53	0.09– 0.97	0.018	0.21	-0.19– 0.60	0.308
Reading	0.03	-0.27– 0.33	0.833	0.54	0.02– 1.07	0.044	0.17	-0.24– 0.58	0.424
Math	-0.01	-0.37– 0.34	0.943	0.25	-0.28– 0.78	0.358	0.08	-0.46– 0.78	0.784
	*r*C	CI	*p*	*r*C	CI	*p*	*r*C	CI	*p*
Processing speed	-1	-1 – -1	0.000	0.29	-0.43– 1	0.436	-0.33	-1.38–0.71	0.533
Executive functions	-1	-1 – -1	0.000	0.24	-0.79– 1.27	0.649	-0.96	-2.74 – 0.81	0.286
Perceptual reasoning	0.60	0.47– 0.72	0.000	-1	-1 – -1	0.000	-1	-1 – -1	0.000
Verbal comprehension	1	1 – 1	0.000	-0.13	-0.92– 0.66	0.741	-1	-1 – -1	0.000
Reading	-1	-1 – -1	0.000	-1	-1 – -1	0.000	-1	-1 – -1	0.000
Math	-1	-1 – -1	0.000	0.15	-0.73– 1.03	0.734	-0.68	-2.22– 1.35	0.390
	*r*E	CI	*p*	*r*E	CI	*p*	*r*E	CI	*p*
Processing speed	-0.08	-0.38– 0.22	0.619	0.21	-0.14– 0.56	0.235	0.14	-0.17– 0.44	0.392
Executive functions	0.07	-0.07 – 0.21	0.328	0.10	-0.07– 0.27	0.241	0.01	-0.16 – 0.17	0.919
Perceptual reasoning	0.04	-0.08 – 0.16	0.500	-0.01	-0.12 – 0.12	0.950	0.01	-0.10– 0.12	0.870
Verbal comprehension	-0.02	-0.14– 0.09	0.701	-0.06	-0.19 – 0.07	0.403	0.01	-0.13 – 0.13	0.964
Reading	0.02	-0.16– 0.20	0.834	-0.17	-0.35– 0.02	0.074	-0.04	-0.23 – 0.16	0.727
Math	-0.02	-0.19 – 0.15	0.825	-0.01	-0.21– 0.19	0.927	0.05	-0.19– 0.29	0.699

Regression coefficients, 95% confidence intervals (CIs), and *p*-value calculated in a bivariate biometric model that decomposed the association between DNA-methylation and cognition into components representing additive genetic factors (*A*), environmental factors shared by twins living in the same home (*C*), and environmental factors unique to each twin (*E*). *r*A is the correlation between the *A* components of variation in DNA-methylation and cognition, which reflects the extent to which genetic variation in DNAm accounts for differences in cognitive functioning. *r*C is the correlation between the *C* components of variation in DNA-methylation and cognition, which reflects the extent to which shared environmental variation in DNAm accounts for differences in cognitive functioning. *r*E is the correlation between the *E* components of variation in DNA-methylation and cognition, which reflects the extent to which identical twins who differ from their co-twins in DNAm show corresponding differences in their cognitive functioning.
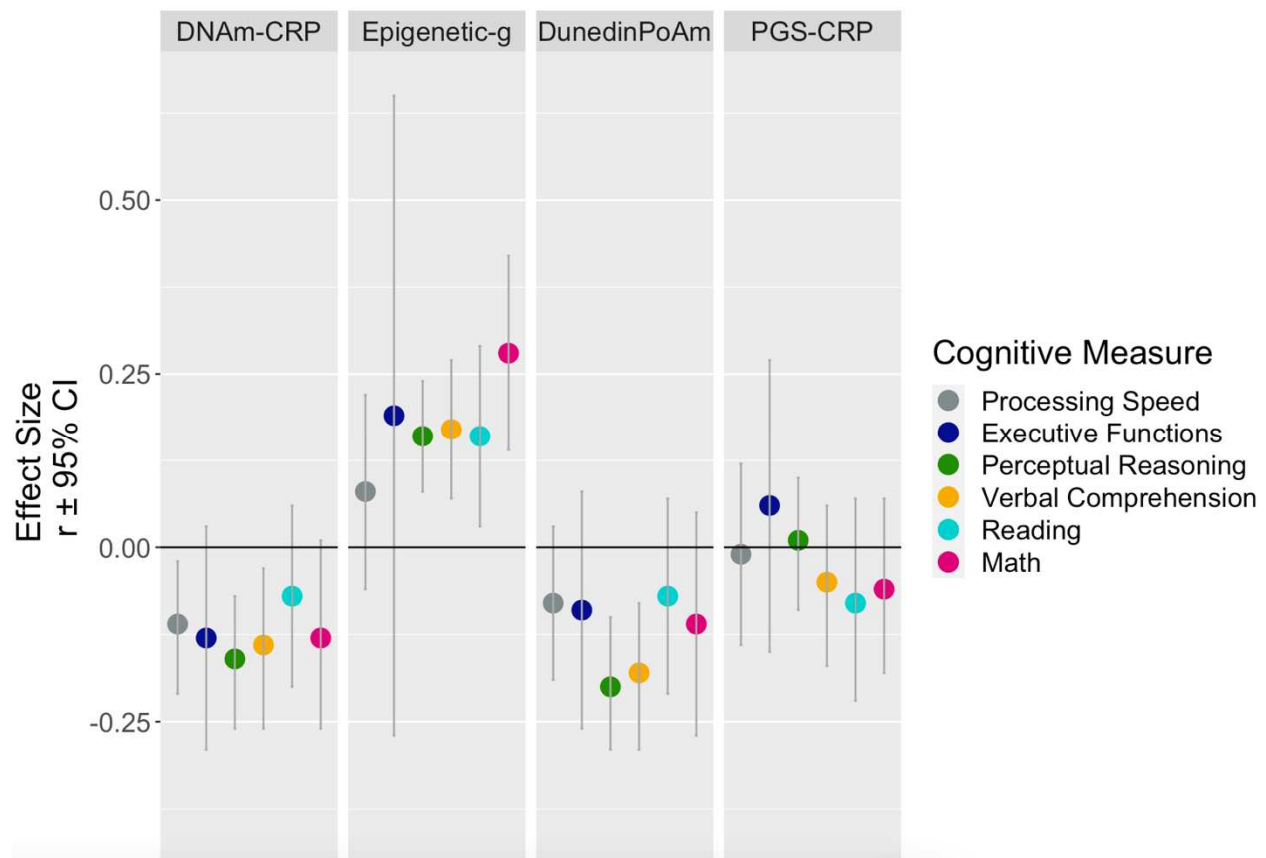
Figure S1. **Associations between three DNA-methylation profiles (DNAm-CRP, Epigenetic-g, and DunedinPoAm) and a polygenic score of inflammation (PGS-CRP) with six measures of cognitive functioning in children and adolescents with listwise deletion.** The plot depicts the standardized regression coefficients (r) and 95% confidence intervals (CIs) calculated by regressing cognitive functions on DNA-methylation measures and PGS-CRP, separately with listwise deletion. PGS analyses were restricted to participants solely of recent European ancestries as indicated by genetic ancestry PCs that are comparable to the GWAS discovery sample. All models included covariate adjustment for child's age and gender, and technical covariates. Higher cognitive values indicate higher task performance. Higher DNAm-CRP and PGS-CRP values indicate a methylation profile and genetic profile of higher chronic inflammation, respectively. Higher Epigenetic-g values indicate a methylation profile associated with higher cognitive functioning. Higher DunedinPoAm values indicate a methylation profile of faster biological aging.

References

1. E. M. Tucker-Drob, Cognitive Aging and Dementia: A Life-Span Perspective. *Annu. Rev. Dev. Psychol.* **1**, 177–196 (2019).

2. L. E. Engelhardt, J. A. Church, K. P. Harden, E. M. Tucker□Drob, Accounting for the shared environment in cognitive abilities and academic achievement with measured socioecological contexts. *Developmental Science* **22**, e12699 (2019).

3. K. M. Korous, J. M. Causadias, R. H. Bradley, S. S. Luthar, R. Levy, A Systematic Overview of Meta-Analyses on Socioeconomic Status, Cognitive Ability, and Achievement: The Need to Focus on Specific Pathways. *Psychol Rep*, 003329412098412 (2020).

4. D. M. Anglin, *et al.*, From Womb to Neighborhood: A Racial Analysis of Social Determinants of Psychosis in the United States. *AJP*, appi.ajp.2020.2 (2021).

5. N. Krieger, Measures of Racism, Sexism, Heterosexism, and Gender Binarism for Health Equity Research: From Structural Injustice to Embodied Harm—An Ecosocial Analysis. *Annu. Rev. Public Health* **41**, 37–62 (2020).

6. D. R. Williams, N. Priest, N. B. Anderson, Understanding associations among race, socioeconomic status, and health: Patterns and prospects. *Health Psychology* **35**, 407–411 (2016).

7. A. Danese, S. J Lewis, Psychoneuroimmunology of Early-Life Stress: The Hidden Wounds of Childhood Trauma? *Neuropsychopharmacol* **42**, 99–114 (2017).

8. N. Snyder-Mackler, *et al.*, Social determinants of health and survival in humans and other animals. *Science* **368**, eaax9553 (2020).

9. S. Ligthart, *et al.*, DNA methylation signatures of chronic low-grade inflammation are associated with complex diseases. *Genome Biology* **17**, 255 (2016).

10. S. Horvath, K. Raj, DNA methylation-based biomarkers and the epigenetic clock theory of ageing. *Nature Reviews Genetics* **19**, 371–384 (2018).

11. D. L. McCartney, *et al.*, "Blood-based epigenome-wide analyses of cognitive abilities" (Genetic and Genomic Medicine, 2021) https:/doi.org/10.1101/2021.05.24.21257698 (May 31, 2021).

12. K. M. Bakulski, A. Halladay, V. W. Hu, J. Mill, M. D. Fallin, Epigenetic Research in Neuropsychiatric Disorders: the "Tissue Issue." *Curr Behav Neurosci Rep* **3**, 264–274 (2016).

13. L. Raffington, *et al.*, Socioeconomic Disadvantage and the Pace of Biological Aging in Children. *Pediatrics*, e2020024406 (2021).

14. A. J. Stevenson, *et al.*, Characterisation of an inflammation-related epigenetic score and its association with cognitive ability. *Clinical Epigenetics* **12** (2020).

15. E. D. Barker, *et al.*, Inflammation-related epigenetic risk and child and adolescent mental health: A prospective study from pregnancy to middle adolescence. *Dev Psychopathol* **30**, 1145–1156 (2018).

16. D. Belsky, *et al.*, Quantification of the pace of biological aging in humans through a blood test: The DunedinPoAm DNA methylation algorithm. *eLife* **9** (2020).

17. S. Ligthart, *et al.*, Genome Analyses of >200,000 Individuals Identify 58 Loci for Chronic Inflammation and Highlight Pathways that Link Inflammation and Complex Disorders. *The American Journal of Human Genetics* **103**, 691–706 (2018).

18. B. J. Goosby, J. E. Cheadle, C. Mitchell, Stress-related biosocial mechanisms of discrimination and African American health inequities. *Annual Review of Sociology* **44**, 319–340 (2018).

19. D. Card, L. Giuliano, Universal screening increases the representation of low-income and minority students in gifted education. *Proceedings of the National Academy of Sciences* **113**, 13678–13683 (2016).

20. , "2019 National healthcare quality and disparities report" (Agency for Healthcare Research and Quality, 2020).

21. S. O. Roberts, C. Bareket-Shavit, F. A. Dollins, P. D. Goldie, E. Mortenson, Racial Inequality in Psychological Research: Trends of the Past and Recommendations for the Future. *Perspectives on Psychological Science* **15**, 1295–1309 (2020).

22. L. Y. M. Middleton, *et al.*, Saliva cell type DNA methylation reference panel for epidemiological studies in children. *Epigenetics*, 1–17 (2021).

23. K. P. Harden, E. M. Tucker-Drob, J. L. Tackett, The Texas Twin Project. *Twin Research and Human Genetics* **16**, 385–390 (2013).

24. M. J. Aryee, *et al.*, Minfi: A flexible and comprehensive Bioconductor package for the analysis of Infinium DNA methylation microarrays. *Bioinformatics* (2014) https:/doi.org/10.1093/bioinformatics/btu049.

25. T. J. Triche, D. J. Weisenberger, D. Van Den Berg, P. W. Laird, K. D. Siegmund, Low-level processing of Illumina Infinium DNA Methylation BeadArrays. *Nucleic Acids Research* **41**, e90–e90 (2013).

26. R. Pidsley, *et al.*, Critical evaluation of the Illumina MethylationEPIC BeadChip microarray for whole-genome DNA methylation profiling. *Genome Biology* **17**, 208 (2016).

27. W. E. Johnson, C. Li, A. Rabinovic, Adjusting batch effects in microarray expression data using empirical Bayes methods. *Biostatistics* **8**, 118–127 (2007).

28. D. W. Belsky, Reply to Newman: Quantification of biological aging in young adults is not the same thing as the onset of obesity. *Proceedings of the National Academy of Sciences* **112**, E7164–E7165 (2015).

29. C. A. Anderson, *et al.*, Data quality control in genetic case-control association studies. *Nat Protoc* **5**, 1564–1573 (2010).

30. S. Turner, *et al.*, Quality Control Procedures for Genome-Wide Association Studies. *Current Protocols in Human Genetics* **68**, 1.19.1-1.19.18 (2011).

31. N. R. Roshyara, H. Kirsten, K. Horn, P. Ahnert, M. Scholz, Impact of pre-imputation SNP-filtering on genotype imputation results. *BMC Genetics* **15**, 88 (2014).

32. A. Auton, *et al.*, A global reference for human genetic variation. *Nature* **526**, 68–74 (2015).

33. L. R. Lloyd-Jones, *et al.*, Improved polygenic prediction by Bayesian multiple regression on summary statistics. *Nature Communications* **10**, 5086 (2019).

34. O. Pain, *et al.*, Evaluation of polygenic prediction methodology within a reference-standardized framework. *PLoS Genet* **17**, e1009021 (2021).

35. The International HapMap 3 Consortium, Integrating common and rare genetic variation in diverse human populations. *Nature* **467**, 52–58 (2010).

36. C. C. Chang, *et al.*, Second-generation PLINK: rising to the challenge of larger and richer datasets. *GigaScience* **4**, 7 (2015).

37. D. Wechsler, Wechsler intelligence scale for children–Fourth Edition (WISC-IV). *San Antonio, TX: The Psychological Corporation* (2003).

38. T. A. Salthouse, R. L. Babcock, Decomposing adult age differences in working memory. *Developmental Psychology* **27**, 763–766 (1991).

39. I. Wright, M. Waterman, H. Prescott, D. Murdoch□Eaton, A new Stroop-like measure of inhibitory function development: typical developmental trends. *Journal of Child Psychology and Psychiatry* **44**, 561–575 (2003).

40. K. Lee, R. Bull, R. M. H. Ho, Developmental Changes in Executive Functioning. *Child Development* **84**, 1933–1953 (2013).

41. G. D. Logan, R. J. Schachar, R. Tannock, Impulsivity and Inhibitory Control. *Psychol Sci* **8**, 60–64 (1997).

42. F. Verbruggen, G. D. Logan, M. A. Stevens, STOP-IT: Windows executable software for the stop-signal paradigm. *Behavior Research Methods* **40**, 479–483 (2008).

43. T. A. Salthouse, What cognitive abilities are involved in trail-making performance? *Intelligence* **39**, 222–232 (2011).

44. A. Miyake, *et al.*, The Unity and Diversity of Executive Functions and Their Contributions to Complex "Frontal Lobe" Tasks: A Latent Variable Analysis. *Cognitive Psychology* **41**, 49–100 (2000).

45. C. L. Baym, B. A. Corbett, S. B. Wright, S. A. Bunge, Neural correlates of tic severity and cognitive control in children with Tourette syndrome. *Brain* **131**, 165–179 (2008).

46. M. J. Kane, *et al.*, The Generality of Working Memory Capacity: A Latent-Variable Approach to Verbal and Visuospatial Memory Span and Reasoning. *Journal of Experimental Psychology: General* **133**, 189–217 (2004).

47. M. Daneman, P. A. Carpenter, Individual differences in working memory and reading. *Journal of verbal learning and verbal behavior* **19**, 450–466 (1980).

48. J. M. Broadway, R. W. Engle, Validating running memory span: Measurement of working memory capacity and links with fluid intelligence. *Behavior Research Methods* **42**, 563–570 (2010).

49. S. M. Jaeggi, *et al.*, The relationship between n-back performance and matrix reasoning — implications for training and transfer. *Intelligence* **38**, 625–635 (2010).

50. L. E. Engelhardt, D. A. Briley, F. D. Mann, K. P. Harden, E. M. Tucker-Drob, Genes unite executive functions in childhood. *Psychological Science* **26**, 1151–1163 (2015).

51. L. E. Engelhardt, *et al.*, Strong genetic overlap between executive functions and intelligence. *Journal of Experimental Psychology: General* **145**, 1141–1159 (2016).

52. D. Wechsler, *Wechsler Abbreviated Scale of Intelligence--Second Edition (WASI-II)* (2011) https:/doi.org/citeulike-article-id:6135820.

53. R. W. Woodcock, K. S. McGrew, N. Mather, *Woodcock-Johnson III Tests of Achievement* (Riverside Publishing, 2001).

54. U. D. of A. E. R. Service, "US Household Food Security Survey Module: three-stage design, with screeners." (2012).

55. R. Chetty, J. N. Friedman, N. Hendren, M. R. Jones, S. R. Porter, "The Opportunity Atlas: Mapping the Childhood Roots of Social Mobility" (National Bureau of Economic Research, 2018) https:/doi.org/10.3386/w25147 (March 26, 2021).

56. A. Datar, P. J. Chung, Changes in Socioeconomic, Racial/Ethnic, and Sex Disparities in Childhood Obesity at School Entry in the United States. *JAMA Pediatr* **169**, 696 (2015).

57. S. Wahl, *et al.*, Epigenome-wide association study of body mass index, and the adverse outcomes of adiposity. *Nature* **541**, 81–86 (2017).

58.   N. L. Colich, M. L. Rosen, E. S. Williams, K. A. McLaughlin, Biological Aging in Childhood and Adolescence Following Experiences of Threat and Deprivation: A Systematic Review and Meta-Analysis. *Psychological Bulletin* **146**, 721–764 (2020).

59.   K. Almstrup, *et al.*, Pubertal development in healthy children is mirrored by DNA methylation patterns in peripheral blood. *Scientific Reports* **6**, 28657 (2016).

60.   C. F. Aylwin, C. A. Toro, E. Shirtcliff, A. Lomniczi, Emerging Genetic and Epigenetic Mechanisms Underlying Pubertal Maturation in Adolescence. *J Res Adolesc* **29**, 54–79 (2019).

61.   A. C. Petersen, L. Crockett, M. Richards, A. Boxer, A self-report measure of pubertal status: Reliability, validity, and initial norms. *Journal of youth and adolescence,* **17**, 117–133 (1988).

62.   US Department of Health and Human Services (USDHHS)(2012).

63.   R. Joehanes, *et al.*, Epigenetic signatures of cigarette smoking. *Circulation: Cardiovascular Genetics* **9**, 436–447 (2016).

64.   B. R. Joubert, *et al.*, DNA Methylation in Newborns and Maternal Smoking in Pregnancy: Genome-wide Consortium Meta-analysis. *American Journal of Human Genetics* **98**, 680–696 (2016).

65.   L. K. Muthén, B. O. Muthén, *Mplus User's Guide*, Muthén & Muthén, Ed., Eighth Edi (2017).

66.   Y. Benjamini, Y. Hochberg, Controlling the False Discovery Rate☐: A Practical and Powerful Approach to Multiple Testing. *Journal of the Royal Statistical Society* **57**, 289–300 (1995).