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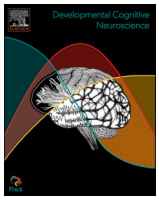

Brain structures with stronger genetic associations are not less associated with family- and state-level economic contexts

Camille M. Williams [a,*], David G. Weissman [b,c], Travis T. Mallard [d,e,f], Katie A. McLaughlin [g], K. Paige Harden [a]

[a] Department of Psychology and Population Research Center, University of Texas at Austin, USA
[b] Department of Psychology, California State University, Dominguez Hills, USA
[c] Department of Psychology, Harvard University, California State University, Dominguez Hills, USA
[d] Psychiatric and Neurodevelopmental Genetics Unit, Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA, USA
[e] Department of Psychiatry, Harvard Medical School, Boston, MA, USA
[f] Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, Boston, MA, USA
[g] Department of Psychology, Harvard University, USA

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ABSTRACT

We investigate whether neural, cognitive, and psychopathology phenotypes that are more strongly related to genetic differences are less strongly associated with family- and state-level economic contexts (N = 5374 individuals with 1KG-EUR-like genotypes with 870 twins, from the Adolescent Behavior and Cognitive Development study). We estimated the twin- and SNP-based heritability of each phenotype, as well as its association with an educational attainment polygenic index (EA PGI). We further examined associations with family socioeconomic status (SES) and tested whether SES-related differences were moderated by state cost of living and social safety net programs (Medicaid expansion and cash assistance). SES was broadly associated with cognition, psychopathology, brain volumes, and cortical surface areas, even after controlling for the EA PGI. Brain phenotypes that were more heritable or more strongly associated with the EA PGI were not, overall, less related to SES, nor were SES-related differences in these phenotypes less moderated by macroeconomic context and policy. Informing a long-running theoretical debate, and contra to widespread lay beliefs, results suggest that aspects of child brain development that are more strongly related to genetic differences are not, in general, less associated with socioeconomic contexts and policies.

1. Introduction

Genetic differences are associated with differences in nearly every aspect of child development, including brain structure and function, as well as with symptoms of psychopathology and cognitive abilities (Blokland et al., 2012; Polderman et al., 2015). Some social scientists have argued that, if genetic differences substantially contribute to variation in child development, then interventions and policies aiming to improve cognition, academic achievement, well-being, or behavior problems will generally be ineffective (Jensen, 1969; Murray, 2020). Relatedly, some evolutionary biologists have proposed a trade-off between how heritable a trait is (i.e., how much variation in a trait is due to genetic differences) and how plastic the trait is to changes in environmental context (Tonsor et al., 2013). And, among the lay public, the belief that there are "biogenetic" influences on a trait or behavior is associated with greater pessimism about the possibility of change (Haslam and Kvaale, 2015; Lebowitz and Appelbaum, 2019). In contrast, other theorists have emphasized that even very highly heritable phenotypes can, in some cases, be intervened upon environmentally, as the examples of shortsightedness and phenylketonuria illustrate (Burt et al., 2019; Goldberger, 1979; Harden, 2021; Haworth and Davis, 2014). But are these exceptions that prove the rule? Few studies have empirically investigated whether aspects of child development that are more strongly associated with genetic differences are, on average, less responsive to differences in environmental context. Here, using data from the Adolescent Behavior and Cognitive Development (ABCD) study, we test whether brain structure, cognitive, and psychopathology phenotypes that are more strongly associated with genetic differences

* Corresponding author at: Department of Psychology and Population Research Center, University of Texas at Austin, USA.
E-mail address: williams.m.camille@gmail.com (C.M. Williams).

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between children are, on average, less associated with parental socioeconomic status (SES) and whether SES-related differences in these phenotypes are less moderated by state-level economic contexts and policies.

The few studies that have investigated whether phenotypes with stronger genetic associations are less responsive to environmental changes have used twin designs and yielded mixed conclusions. Twin designs estimate heritability by leveraging theoretical differences in genetic relatedness between monozygotic and dizygotic twins, asking whether monozygotic twins are more phenotypically similar than dizygotic twins. An early twin study of attitude change found that people showed greater physiological stress following interventions targeting more heritable compared to less heritable attitudes, and that average intervention effects were smaller as the heritability of the attitude increased (Tesser et al., 1998). In contrast, two twin studies reported that brief in-laboratory manipulations (namely, an acute psychosocial stressor test and a growth mindset intervention) produced marked changes in physiological and psychological phenotypes (cortisol output and growth mindset, respectively) irrespective of their heritability estimates (Burgoyne et al., 2020; Raffington et al., 2022).

In addition to twin data, genetic associations with a phenotype can be estimated from data that directly measure genomic variants, most commonly single nucleotide polymorphisms (SNPs). Genomic heritability studies leverage differences in measured genomic similarity across SNPs between pairs of unrelated individuals, asking whether people who are more genetically similar are also more phenotypically similar. Whereas twin heritability estimates are putatively based on all forms of genetic variation, SNP heritability estimates are solely based on common genetic variants (Young, 2019). Yet another method for estimating genetic associations is to use a polygenic index (PGI), which leverages results from large-scale genome-wide association studies on SNPs to create a summary measure of an individual's overall genetic liability for a given trait (Choi et al., 2020).

Of particular interest to child development researchers is the educational attainment (EA) PGI, which can now be calculated from the results of a genome-wide association study of years of completed formal schooling in over 3 million people (all of whom were most similar, genetically, to reference panels of people sampled from Europe, relative to people sampled from other regions of the world) (Okbay et al., 2022). Prior studies reported that the EA PGI is robustly correlated with children's brain structure, cognition, and academic achievement, as well as with SES, both within and between families (e.g., Isungset et al., 2022; Merz et al., 2022; Okbay et al., 2022). Some studies have found limited overlap between the brain regions associated with SES and those associated with the EA PGI in adolescents (Judd et al., 2020; Merz et al., 2022), but a larger study in adults revealed substantial convergence between brain regions associated with SES and an EA PGI (Kweon et al., 2022).

In this study, we use all three methods – twin modeling, SNP heritability, and PGI – to add to the small empirical literature examining whether phenotypes that are more strongly associated with genetic differences between people are, as has been hypothesized, generally less responsive to economic context. The ABCD study is an ideal dataset to test this hypothesis as it includes twins, genomic data, neuroimaging data, cognitive and psychopathology measures, and a range of individual and state-level environmental variables. Previous research with the ABCD study has documented that many aspects of brain development, as well as internalizing and externalizing psychopathology symptoms and cognitive abilities, are associated with adolescent's environmental context, including parental SES (Dennis et al., 2022; Judd et al., 2020; Taylor et al., 2020). These SES-related differences in adolescent development might be moderated by macroeconomic contexts and policies, including social safety net programs which are designed to provide financial assistance, support, and resources to low-income individuals and households (Bitler et al., 2017). For instance, SES-related differences in hippocampal volume and internalizing symptoms were found to be moderated by state-level average cost of living and by two safety net programs: Medicaid expansion after the passage of the Affordable Care Act in 2010 and average cash assistance to low-income households (Weissman et al., 2023). The ABCD study thus provides a unique opportunity to examine whether genetic measures of a phenotype are correlated with the phenotype's association with individual economic context and the moderation of SES by macroeconomic contexts and policies, which differ between US states.

This study provides a more comprehensive examination of how variation across adolescent neurobiological phenotypes in the strength of their genetic associations is related, or unrelated to their associations with economic contexts and policies in the US. This relationship, between the parameters estimated from genetic analyses and those estimated from analyses of variation across socioeconomic contexts, has long been an object of theoretical speculation and public interest but has rarely been investigated empirically as we do here.

2. Methods

The preregistration and code are available here: osf.io/mg63h.

2.1. Sample

The Adolescent Brain and Cognitive Development (ABCD) study is a longitudinal cohort study that enrolled 11,876 youth at baseline across 21 sites in 17 US states. Mental and physical health were assessed at annual visits (Volkow et al., 2018; https://abcdstudy.org/). The sample includes 840 pairs of same-sex twins recruited from state birth registries at four sites (Garavan et al., 2018). ABCD study imaging procedures were harmonized across sites (Casey et al., 2018). The study protocols were approved by the University of California, San Diego Institutional Review Board. The data used in this study were obtained from the year 1 assessment (data release 4.0).

Regression analyses were conducted on a maximum of 5370 individuals (mean age = 9.925 years, SD = 0.631, N females = 2559) who: (1) identified as white and non-Hispanic; (2) had genotypes most similar to the 1000 Genomes EUR reference panel ("1KG-EUR-like" individuals), as compared to people sampled from other regions of the world; (3) had available demographic data; and (4) had data on at least one cognition, psychopathology, or neuroimaging measure. The number of participants included in the regression analyses differed across investigated phenotypes, ranging from N = 5189 to 5370 (Supplemental Material). To facilitate comparisons between twin- and SNP-based estimates of heritability, we performed analyses on a subset of same-sex twins with 1KG-EUR-like genotypes, including a maximum of 382 MZ (N females = 190) and 492 DZ twins (N females = 236; Supplemental Table 1).

2.2. Measures

2.2.1. Polygenic index

We calculated an educational-attainment PGI (EA PGI) using results from the EA genome-wide association study (GWAS) on 3 million individuals, including data from 23andMe, Inc. (Okbay et al., 2022). Participant inclusion, genotyping, imputation, principal component analyses, and quality checks are described in the Supplemental Material. Briefly, PGIs were computed using PRS-CS, a Bayesian approach that incorporates all SNPs (*i.e.*, no p-value thresholding) and uses an external linkage disequilibrium reference panel to account for correlations between SNPs (Ge et al., 2019).

2.2.2. Demographics

Demographic variables included self-reported age, biological sex, genomic principal components, and socioeconomic status (SES) as measured by the income-to-needs ratio. To calculate income-to-needs ratio, caregivers selected one of the ten income ranges, and the

midpoint of the range was selected as the family income for each participant. The ratio was calculated by dividing the family income by the 2017 federal poverty threshold for a family of that size (U.S. Census Bureau, 2022; Supplemental Table 2). We chose the income-to-needs ratio over other indicators of socioeconomic status (e.g., parental education) as it was hypothesized to be most affected by state-level economic policies and contexts. Following previous analyses of this sample (Weissman et al., 2023) (Weissman et al., 2023), we applied a natural log to the income-to-needs ratio (Supplemental Material). Extensive work suggests that the relationship of income with human phenotypes is best modeled as log-linear rather than linear (Noble et al., 2015; Rosen et al., 2018, 2020).

2.2.3. Brain structure

We conducted analyses on 164 neuroimaging phenotypes generated by the ABCD study (Hagler et al., 2019): 68 cortical mean thicknesses, 68 cortical surface areas, 17 subcortical grey matter volumes, and 11 other brain volumes (i.e., corpus callosal volumes, cerebellar grey and white matter volumes, and whole brain white matter volumes). All brain segmentations were performed using FreeSurfer v5.3 on T1-weighted MRI volumes. Additional global measures included total brain volume (TBV), total cortical surface area (TSA), and total mean cortical thickness (TMCT). Cortical measures were segmented using the Desikan-Killiany atlas (Desikan et al., 2006) implemented in Freesurfer (Fischl, 2012).

We evaluated the distribution of genetic and SES associations across cortical mean thicknesses and surface areas in comparison with three parcellations of the cortex: (1) the sensorimotor-axis ranking defined by Syndor and colleagues (Sydnor et al., 2021), which reflects cortical development based on macrostructural, microstructural, functional, metabolic, and transcriptomic features; (2) the cytoarchitectonic classes defined by von Economo and Koskinas (Economo and Koskinas, 1925), which categorize cortical regions based on cellular composition and arrangement; and (3) the functional networks derived by Yeo and Krienen (Yeo et al., 2011), which group cortical regions by their involvement in coordinated neural activities. We measured the correlation between the sensorimotor-axis ranking and SES and genetic associations using a Spearman correlation test and tested differences in the distribution of SES and genetic associations across functional networks and cytoarchitectonic classes using a Kruskal-Wallis test. P values were calculated using a spin permutation test (Supplemental Material).

2.2.4. Cognitive ability

Given that fluid and crystallized measures of cognitive ability differ slightly in their genetic architectures (de la Fuente et al., 2021), we included both fluid and crystallized measures of cognitive ability provided by the NIH Toolbox (Supplemental Material).

2.2.5. Psychopathology

Internalizing and externalizing behaviors were measured with parent reports on the school-age version of the Child Behavior Checklist (CBCL) (Achenbach and Rescorla, 2001), a validated DSM-oriented scale. The ABCD study provided CBCL composite scores for internalizing and externalizing behaviors for participants who responded to any of the 112 items, regardless of missingness (Supplemental Material). We log-transformed the raw composite scores as they were right-skewed.

2.2.6. State-level economic context and policies

As previously described (Weissman et al., 2023), we calculated state-level economic context and policies. State-level economic context was measured by the state's cost of living based on Regional Price Parity (RPP) for the year 2017 – the median year in which the ABCD baseline data was collected – and obtained from the U.S. Bureau of Economic Analysis. State-level economic policies were assessed by economic policies, including cash assistance and Medicaid expansion. The state's mean cash assistance program was measured as the mean of the average monthly Earned Income Tax Credit (EITC) and Temporary Assistance for Needy Families (TANF) benefit in each state (Supplemental Material). Medicaid expansion was measured as a dichotomous variable indicating whether that state had expanded Medicaid eligibility through the Affordable Care Act by the end of 2017.

2.3. Statistical analyses

Analyses were conducted in three steps in R (R Core Team 2022). First, we estimated twin and SNP heritabilities, and the associations of the EA PGI with brain, psychopathology, and cognitive outcomes. Second, we investigated the association of SES with each brain, psychopathology, and cognitive outcome, with and without adjusting for the EA PGI. We then tested whether the magnitude of SES-related disparities in outcomes varied across states. For regions that did show variation across states, we examined whether state-level economic context and policies moderated the SES-outcome association. Third, we examined the convergence between results of genetic and SES analyses: do outcomes that show higher heritabilities and/or stronger associations with measured genotypes show weaker associations with SES and/or less moderation of SES by economic policies and contexts?

Regression analyses were conducted using linear mixed-effects models with the *lmerTest* package (Kuznetsova et al., 2017). We controlled for age, sex (genetic sex: males coded −0.5 and females 0.5), age*sex, study site (random intercept), and family ID (random intercept). Brain-related analyses were conducted with the MRI manufacturer as a categorical covariate (0: Siemens, N= 3440; 1: GE Medical Systems, N=1061; 2: Philips Medical systems, N = 688). We ran the analyses of regional brain phenotypes with and without adjusting for the region's global measure (i.e., TBV for volumes, TSA for surface areas, and TMCT for mean thicknesses). The first ten ancestral principal components were included as covariates across analyses including the EA PGI as a fixed effect.

We report results in the main text that are significant ($p < 0.05$) after applying a False Discovery Rate (FDR) correction to the p values of the coefficients of interest in each analysis (Supplemental Material). The p value significance threshold for global brain measures was set to 0.05/3. All betas and standard errors (SE) are standardized and can be interpreted as the change in SD of the cognition, brain, or psychopathology phenotype for a change of 1 SD in the predictor variable (e.g., SES).

2.3.1. Genetic analyses

We estimated twin heritability with a 2-group Cholesky ACE twin model using the *umx* package (Bates et al., 2019). The ACE model estimates the proportions of total phenotypic variation that is due to variation in additive genetics (A; i.e., heritability), shared environment, which includes all environmental factors shared by twins raised in the same home that serve to make twins similar to one another regardless of zygosity (C), and non-shared environment (E), which includes all environmental factors that make twins different from one another regardless of zygosity, plus measurement error. We estimated SNP heritability using genome-wide complex trait analysis - genome-based restricted maximum likelihood (GCTA-GREML) on 6303,056 SNPs (Yang et al., 2011). We estimated associations with the EA PGI using linear mixed-effects models.

2.3.2. SES analyses

We estimated associations with SES using linear mixed-effects models. Next, we ran regression models including both SES and the EA PGI, to examine whether the SES-phenotype associations were robust to adjusting for genes associated with educational attainment.

To reduce the number of phenotypes included in moderation analyses with state-level economic context and policies, we first investigated whether the association between SES and each phenotype varied by study site. Given that study sites are distributed across states, variations in the SES association across sites may be driven by state-level

differences in economic context and policy. We conducted a linear mixed effects model that estimated a random slope of SES, and identified which phenotypes had a significant random slope by comparing the fit of the model with and without including SES as a random slope using ANOVA. A significant ANOVA test ($p < 0.05$) indicated that the model with SES as a random slope fit the data better, suggesting that the SES gradient varied by site, and in turn, by state.

Focusing on the subset of phenotypes that showed significant variation in the SES association across states, we then estimated the extent to which the state's economic context (cost of living) and economic policy (i.e., Medicaid Expansion or mean cash assistance) moderated the associations with SES. Both economic policies were positively associated with family SES (Supplemental Material). All models included the main effects of SES, the state's cost of living, and an economic policy (either Medicaid Expansion or the state's mean cash assistance) and their interactions. Coefficients of interest for the multiple comparison corrections included 2- and 3-way interactions. We repeated these analyses adjusting for the EA PGI.

2.3.3. Convergence between results of genetic and SES analyses

The analyses described above produced two estimates of environmental associations with each phenotype: (1) the regression on SES and (2) the moderation of the SES association by economic context and policies (e.g., the regression on a three-way interaction of SES x cost of living x policy). They also produced three estimates of genetic influences: (1) twin heritability, (2) SNP heritability, and (3) regression on the EA PGI.

In our final analysis, we examined the convergence between these parameters. Specifically, we estimated Pearson correlations between the SES regression coefficients (main and interaction effects) and the three genetic parameters. A positive correlation in this analysis would indicate that phenotypes with stronger genetic associations are more strongly associated with SES and/or that their associations with SES are more strongly moderated by state-level economic context and policies. A negative correlation would indicate that phenotypes with stronger genetic associations are less associated with SES and/or less moderated by differences in state-level economic context and policies.

When evaluating the spatial correspondence of cortical maps, we used a permutation-based "spin" test to account for the spatial contiguity and hemispheric symmetry of the cortex (Grotzinger et al., 2023).

We further tested whether correlations between genetic and environmental parameter estimates were driven by differences between phenotypes in measurement error. Specifically, we estimated how genetic and SES parameter estimates related to indicators of measurement reliability, including regional brain size, intraclass correlation coefficients, and test-retest correlation coefficients (Supplemental Material; Supplemental Table 11).

3. Results

3.1. Genetic analyses

3.1.1. Brain, cognition, and psychopathology phenotypes are heritable

Twin heritability estimates were greater than SNP heritability estimates for crystallized ($h^2_{Twin} = 0.61$, $h^2_{SNP} = 0.42$) and fluid ($h^2_{Twin} = 0.52$, $h^2_{SNP} = 0.19$) intelligence and externalizing ($h^2_{Twin} = 0.72$, $h^2_{SNP} = 0.18$) and internalizing ($h^2_{Twin} = 0.19$, $h^2_{SNP} = 0.03$) psychopathology scores.

Twin heritability estimates for brain outcomes ranged from 0.44 to 0.95 for volumes (median $h^2_{Twin} = 0.73$), from 0.22 to 0.78 for cortical surface areas (median $h^2_{Twin} = 0.56$), and from 0.10 to 0.76 for cortical mean thicknesses (median $h^2_{Twin} = 0.52$). SNP heritability estimates were generally smaller than twin estimates, ranging from 0.12 to 0.41 for volumes (median $h^2_{SNP} = 0.29$), from 0.02 to 0.38 for cortical surface areas (median $h^2_{SNP} = 0.17$), and from 0.02 to 0.43 for cortical mean thicknesses (median $h^2_{SNP} = 0.18$; Fig. 1).

Correlations between cortical sensorimotor-axis ranks (Syndor et al., 2021) and the present study's cortical heritability estimates revealed

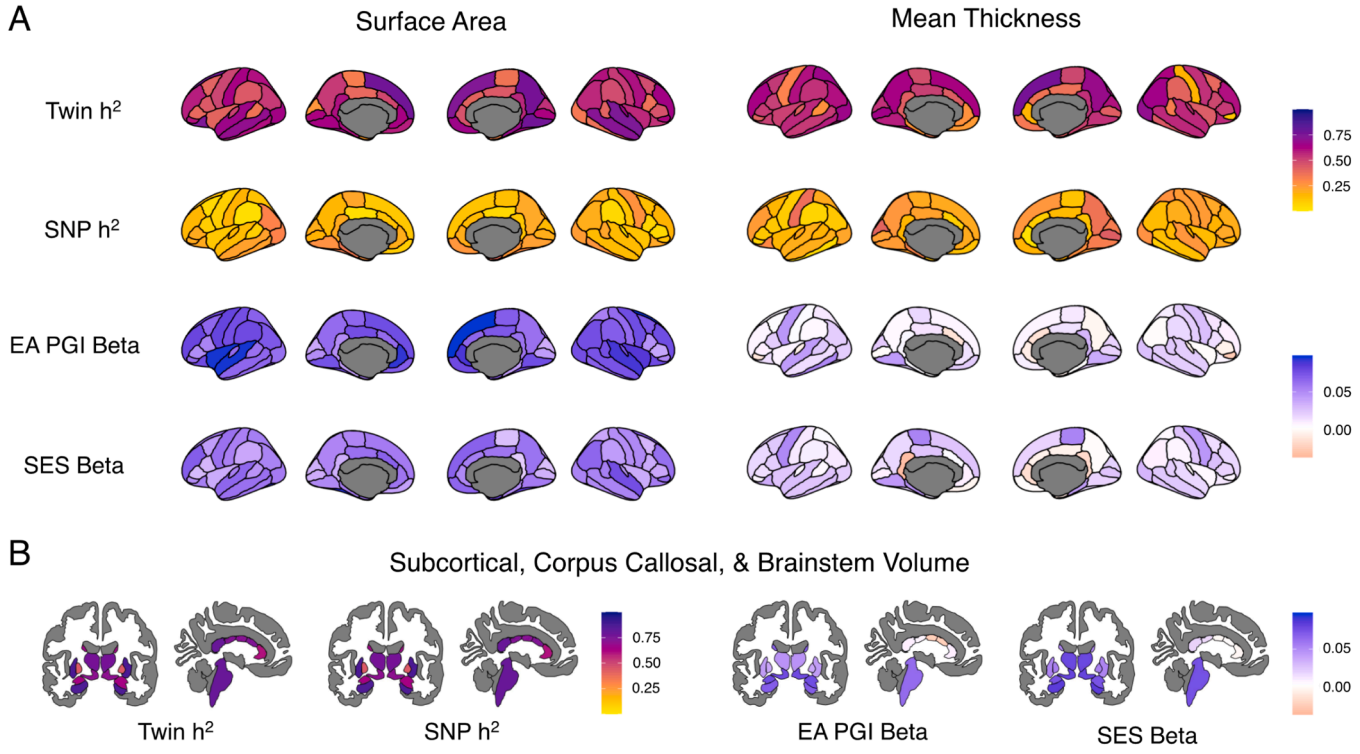

Fig. 1. Distribution of heritabilities, genetic associations, and socioeconomic associations across (A) cortical surface areas and mean thicknesses and (B) volumes. Heritability (h^2) was estimated using twins and single nucleotide polymorphisms (SNPs) estimates. Beta corresponds to the standardized beta from regressions on socioeconomic status (SES) and the educational attainment polygenic index (EA PGI). Associations not adjusted for global brain size.

that mean thicknesses from lower-order, primary, and unimodal cortices with sensory and motor functions were more heritable ($\rho_{Twin} = -0.30$, $\rho_{SNP} = -0.50$) than higher-order transmodal association cortices subserving executive, socioemotional, and mentalizing functions. No association between heritability and sensorimotor-axis rank was found for cortical surface areas (Supplemental Material).

Cortical mean thickness heritability estimates generally varied across cortical functional networks ($p_{Twin} < 0.01$; $p_{SNP} < 0.001$) but did not vary as a function of cortical cytoarchitecture (Supplemental Material). Similar results were observed for SNP heritability and surface areas ($p_{SNP} < 0.001$).

Measures of global brain size (TBV, TSA, and TMCT) were also heritable ($h^2_{Twin} = 0.78$, 0.73, and 0.78, and $h^2_{SNP} = 0.25$, 0.20, and 0.31, respectively; Supplemental Table 3).

3.1.2. Brain, cognition, and psychopathology phenotypes are broadly associated with the EA PGI

Higher EA PGI was associated with higher fluid (β= 0.13, SE = 0.01) and crystallized (β = 0.23, SE = 0.01) intelligence scores and with lower internalizing (β = −0.06, SE = 0.01) and externalizing (β = −0.14, SE = 0.01) scores (Supplemental Table 4).

A higher EA PGI was associated with greater left and right cerebral white matter volume (β = 0.06, SE = 0.01, and β = 0.06, SE = 0.01, respectively) and cerebellar white (β = 0.04, SE = 0.01, and β = 0.04, SE = 0.01) and grey matter volume (β = 0.06, SE = 0.01, for both). Individuals with a higher EA PGI had greater regional size in all subcortical volumes (median |β| = 0.06), all cortical surface areas (median β= 0.07) and were associated with a thicker cortex in 5/68 regions (median β= 0.01; Fig. 1).

Correlations between cortical sensorimotor-axis ranks (Syndor et al., 2021) and the EA PGI beta coefficient indicated that the EA PGI was more strongly related to mean thickness in lower-order regions (sensory and motor functions) compared to higher-order transmodal association regions (executive, socioemotional, and mentalizing functions; $\rho = -0.31$). The opposite pattern was observed for surface area ($\rho = 0.23$). Moreover, associations between the EA PGI and regional mean thicknesses varied as a function of cytoarchitectonic classes ($p < 0.05$), but no such relationship was observed for surface areas (Supplemental Material).

Regarding global measures, the EA PGI was associated with TBV (β= 0.11, SE = 0.01) and TSA (β= 0.10, SE = 0.01) but not TMCT (Supplemental Table 5). Of the 96 brain measures with significant associations with the EA PGI, less than a quarter (17 %, 16/96) were still significant after adjusting for their respective global measure, indicating that the association of the EA PGI with brain structure is largely related to macroscale organization (Supplemental Table 4).

3.1.3. Strength of genetic associations are not primarily driven by differences in measurement reliability

Larger surface areas and mean thicknesses had greater twin heritability estimates ($r = 0.45$ and $r = 0.38$, respectively, spin $p < 0.004$). Larger surface areas were also more strongly associated with the EA PGI (r = 0.35, spin $p < 0.004$). However, genetic parameter estimates were not correlated with regional brain intraclass correlation and test-retest correlation coefficients (Supplemental Material).

3.2. SES analyses

3.2.1. Brain, cognition, and psychopathology phenotypes are broadly associated with SES, even after adjusting for the EA PGI

Higher SES was associated with higher fluid (β= 0.13, SE = 0.02) and crystallized (β = 0.21, SE = 0.01) intelligence scores and with lower internalizing (β = −0.10, SE = 0.01) and externalizing (β = −0.20, SE = 0.01) scores (Supplemental Table 6).

Higher SES was associated with greater left and right brain white matter volume (β = 0.06, SE = 0.01 for both) and cerebellar white (β = 0.06, SE = 0.01 and β = 0.04, SE = 0.01) and grey matter volume (β = 0.08, SE = 0.01, and β = 0.07, SE = 0.01, respectively). Higher SES was also associated with greater regional size in all subcortical volumes (median β = 0.07) and 90 % of cortical surface areas (61/68, median β = 0.06). For mean thicknesses, greater SES was associated with a thicker cortex in only 9/68 regions (median β = 0.05) and a thinner cortex in thickness of the left isthmus of the cingulate gyrus (β = −0.04, SE = 0.02; Fig. 1).

As observed for the EA PGI-cortical associations, the associations of SES with regional brain structure metrics were greater for mean thicknesses and smaller for surface areas in lower-order cortices and varied across cytoarchitectonic classes for mean thicknesses but not surface areas (Supplemental Material).

As observed for the EA PGI-cortical associations, correlations between cortical sensorimotor-axis ranks (Syndor et al., 2021) and SES beta coefficients indicated that the association with SES was greater in mean thicknesses from lower-order cortices ($\rho = -0.24$) and greater in surface areas from higher-order cortices ($\rho = 0.24$). The SES-brain association also only varied across different cytoarchitectonic classes for mean thicknesses ($p < 0.01$; Supplemental Material), but not surface areas.

As for global measures, higher parental SES was associated with greater TBV (β = 0. 09, SE = 0.01) and TSA (β = 0. 08, SE = 0.01) but not with total MCT (Supplemental Table 5). Of the 94 brain measures with significant SES associations, about a quarter (23 %, 22/94) were still significant after adjusting for their respective global measure (Supplemental Table 6).

The EA PGI and SES were modestly correlated with each other ($r = 0.25$) and including both variables as simultaneous predictors did not substantially change the estimated regression coefficients. In models that included both SES and the EA PGI as covariates, associations with SES were generally consistent across phenotypes: SES still was associated with 86 % (84/98) of the regions that were significantly associated with SES before adjusting for the EA PGI, and decreases in effect size were small (median |Δβ| = 0.01). SES was no longer associated with the right caudate volume, the left isthmus cingulate thickness, and 20 % (12/61) of surface areas.

Of the 81 brain measures with significant associations with SES after adjusting for the EA PGI, a quarter (25 %, 20/81) were still significant after adjusting for their respective global measure (Supplemental Table 6; Supplemental Material).

The SES beta was not correlated with any indicator of measurement reliability (Supplemental Material).

3.2.2. State-level economic contexts and policies moderated the association of SES with select volumes and surface areas

Among the phenotypes with a significant association with SES, the association between SES and these phenotypes varied by study site for nine volumes, six surface areas, and one mean thickness (random slope median β = 0.003; Supplemental Table 7). In the next models, we estimated moderation by state-level economic policies and context on these 16 phenotypes.

In the models with mean cash assistance as the state's economic policy, there was a significant 2-way interaction between the state's cost of living and SES for the left and right cerebellar grey matter volumes (Table 1). The association of SES with regional size was greater in high compared to low cost of living states for the left and right cerebellar grey matter volumes (β = 0.04, SE = 0.02, and β = 0.05, SE = 0.02, respectively). After adjusting for the EA PGI and global brain size, the interaction was no longer significant for the left cerebellar grey matter volume and the magnitude of the interaction of both volumes decreased by 10 % (median |Δβ| = 0.002), suggesting that the interaction was not driven by gross neuroanatomical variation (Supplemental Table 8–9).

In regression analyses including Medicaid expansion as the state's economic policy, we observed 2-way interactions between the state's cost of living and SES and between SES and Medicaid expansion, as well

Table 1
Significant moderation of the SES association with brain phenotypes by state-level economic context and policies.

Economic Policy	Region	Coefficient	β	SE	FDR p
Mean cash assistance	left cerebellar grey matter volume	SES x cost of living	0.038	0.018	4.095E−02
	right cerebellar grey matter volume *	SES x cost of living	0.045	0.018	1.269E−02
Medicaid expansion	left cerebral white matter volume	SES x cost of living	0.080	0.028	4.829E−03
		SES x Medicaid expansion x cost of living	−0.084	0.034	1.325E−02
	right cerebral white matter volume	SES x cost of living	0.085	0.028	2.712E−03
		SES x Medicaid expansion x cost of living	−0.079	0.034	1.942E−02
	left thalamus volume	SES x cost of living	0.078	0.029	8.588E−03
		SES x Medicaid expansion x cost of living	−0.098	0.035	5.183E−03
	right ventral diencephalon volume	SES x cost of living	0.060	0.029	4.526E−02
	left cuneus surface area	SES x Medicaid expansion	−0.088	0.035	1.246E−02
	lingual right surface area	SES x Medicaid expansion	−0.087	0.035	1.344E−02
	left pericalcarine surface area	SES x Medicaid expansion	−0.088	0.036	1.516E−02
	right precentral surface area	SES x cost of living	0.068	0.029	1.967E−02
		SES x Medicaid expansion x cost of living	−0.086	0.034	1.311E−02
	right superior frontal surface area	SES x cost of living	0.086	0.030	3.765E−03
		SES x Medicaid expansion	−0.069	0.033	4.149E−02
		SES x Medicaid expansion x cost of living	−0.085	0.035	1.715E−02

N.B. Results from regression models with the interactions of SES, the state's cost of living, and either the state's mean cash assistance or its Medicaid expansion as the state's economic policy. * also significant after adjusting for global brain size. Socioeconomic status (SES). State cost of living. Standardized beta (β).

as 3-way interactions between SES, the state's cost of living, and Medicaid expansion (Table 1). In regions with a significant 2-way interaction between SES and Medicaid (Fig. 2**A**), the association of SES with regional brain size was attenuated in states that expanded Medicaid. In regions with a significant 2-way interaction between SES and cost of living (Fig. 2**B**), the association between SES and regional

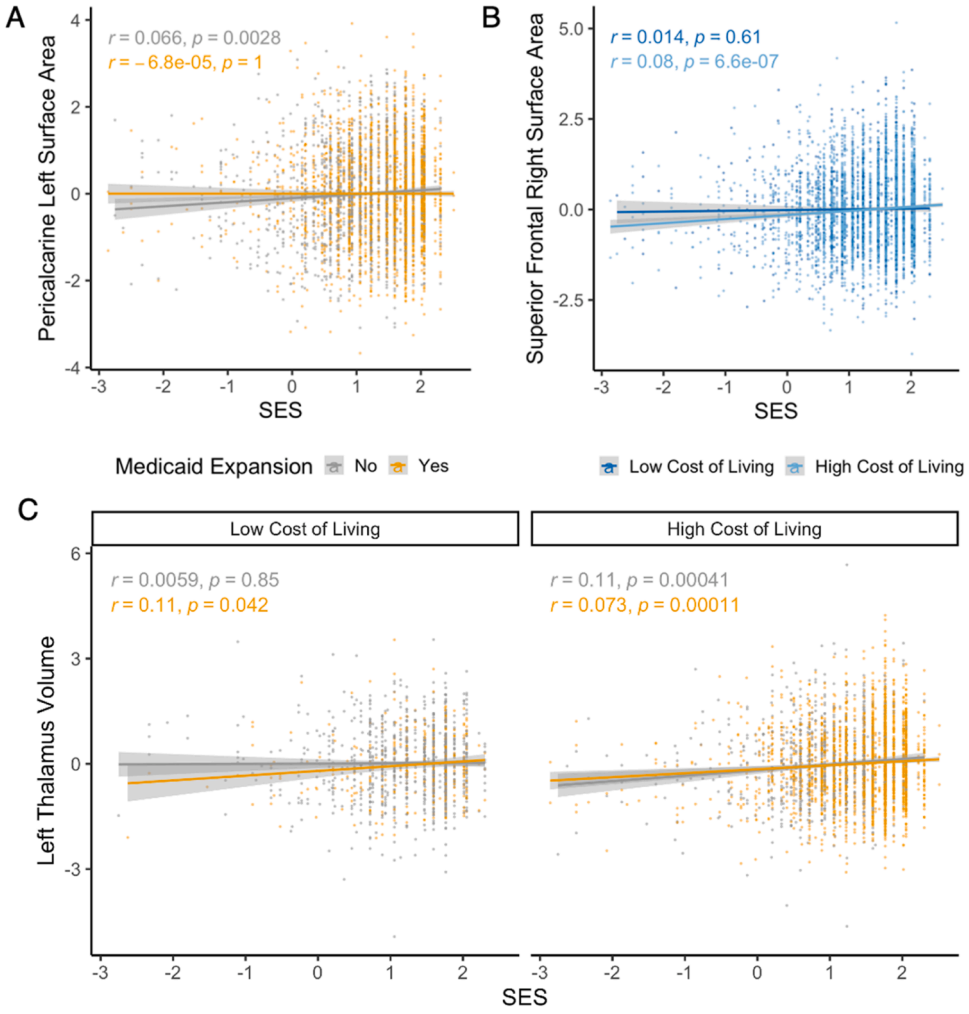

Fig. 2. Largest moderation of socioeconomic status (SES) on brain phenotypes by (A) the state's choice of expanding Medicaid, (B) the state's cost of living, and (C) the state's cost of living and choice of expanding Medicaid. Each point corresponds to an individual. Phenotypes are adjusted for age, sex, age*sex, and the MRI manufacturer, and the random intercepts of the study site and family ID. In panel A, phenotypes are also adjusted for Medicaid expansion, and in panel B for the state's cost of living. Parental socioeconomic status is measured as the log of the income-to-needs ratio (SES).

size was greater in high-cost-of-living states than in low-cost-of-living states. However, for a subset of these regions, including the left thalamus and left and right cerebral white matter volumes, the SES-brain association in high cost-of-living states was attenuated in states that expanded Medicaid (Fig. 2**C,** Supplemental Table 8–9).

3.2.3. Genetic and environmental associations did not correlate across volumes, surface areas, and mean thicknesses

Prior to correcting for global brain size, volumes and mean thicknesses that were more heritable did not show a significantly smaller association with SES, but there was a positive relationship between twin heritability and the SES beta for surface areas (r =.31). There was also a positive association between the SES beta and the EA PGI beta for volumes (r = 0.88) and mean thicknesses (r = 0.43) (Supplemental Material; Table 2).

After adjusting for global brain size, the relationship between the EA PGI beta and the SES beta was attenuated but remained significant and positive for mean thicknesses (r = 0.37) and became significant for surface areas (r = 0.36) but was no longer observed for volumes. Additionally, there was no significant relationship between heritabilities and the magnitude of the SES association after adjusting for global measures, except for a slightly positive relationship between the SES beta and SNP heritability for mean thicknesses (r =.17). (Recall that few mean thicknesses were significantly associated with SES). Overall, brain phenotypes that were more heritable or more strongly associated with the EA PGI were not less associated with SES. Instead, most correlations between genetic associations and SES associations across brain measures were null; the few that were reliably different than zero were positive and substantially driven by global brain size.

Similarly, brain phenotypes that showed stronger policy interactions showed no consistent pattern with respect to heritability or EA PGI associations (Table 2; Supplemental Material). Correlations were only apparent after correcting for global brain size: the two-way interaction between family SES and state cost-of-living was generally closer to zero for more heritable volumes (r ranging from −.51 to −0.53). The three-way interaction with Medicaid expansion was also closer to zero for more heritable volumes (r = 0.54). For mean thicknesses, the opposite pattern was detected, but only for SNP-heritability: More heritable regions showed a stronger two-way interaction between family SES and state economic context. Generally, genetic associations with a phenotype were not consistently correlated with the extent to which the state-level economic context and policies moderated the SES-brain association in the adolescent brain.

4. Discussion

In the present study, we investigated whether adolescent brain phenotypes that were more strongly associated with genetic differences, as estimated from twin heritability, SNP heritability, and PGI analyses, were less related to variation in family- and state-level economic contexts. Contrary to the widespread belief that more genetically associated phenotypes are less plastic in response to environmental differences (Haslam and Kvaale, 2015; Jensen, 1969; Tonsor et al., 2013), we found that brain phenotypes that showed a more pronounced SES gradient, or that showed greater moderation of the SES gradient by macroeconomic context and policy, had no consistent pattern with respect to their heritability estimates or PGI associations. Results might differ, of course, for other developmental phenotypes. These findings contribute to a small literature that provides empirical evidence against the use of heritability estimates or polygenic index associations as the basis for identifying promising targets for intervention (Burgoyne et al., 2020; Haworth and Davis, 2014; Raffington et al., 2022).

Twin studies, SNP-heritability studies, and polygenic index studies rely on different sources of data and make different assumptions (Young, 2019). Twin studies leverage differences in theoretically-implied genetic relatedness between identical versus fraternal twins, and may overestimate heritability due to incorrect assumptions about environmental similarity between twins and unmodeled gene-by-environment interactions and correlations. SNP-heritability studies, on the other hand, likely underestimate genetic influences on a phenotype because they do not capture the effects of rare (unmeasured) genetic variants. Finally, polygenic indices like the EA PGI, when calculated from the results of standard genome-wide association studies, often include "environmental" processes, including population stratification and passive gene-environment correlation, in the estimate of genetic association. There is, consequently, no single "gold-standard" estimate of genetic influence; rather, triangulating across different methods with different limitations and assumptions, as we have done here, is the strongest approach.

Here, we observed some positive correlations between the

Table 2
Correlation between a phenotype's genetic associations and the beta of socio-economic status or the interaction beta of socioeconomic **status** with the state's economic context and/or policy of a phenotype across models with and without adjusting for global brain size.

			Volumes		***Surfaces****		***Mean Thicknesses****	
Regression Model	***Genetic Measure***	***Coefficient***	*Not Adj.*	*Adj.*	*Not Adj.*	*Adj.*	*Not Adj.*	*Adj.*
SES	Twin h^2	SES	0.16	0.04	**0.31**	−0.04	0.20	−0.01
	SNP h^2	SES	−0.05	0.09	0.38	0.29	0.28	**0.17**
	EA PGI	SES	**0.88**	0.19	0.45	**0.36**	**0.43**	**0.37**
Mean Cash Assistance	Twin h^2	SES x COL	0.25	**−0.51**	0.16	−0.09	**0.38**	0.21
	SNP h^2	SES x COL	−0.29	**−0.53**	**−0.22**	−0.12	0.12	0.11
	EA PGI	SES x COL	−0.35	0.03	0.03	−0.12	0.16	0.05
Medicaid Expansion	Twin h^2	SES x COL	0.11	**−0.52**	0.14	−0.02	**0.20**	**0.18**
		SES x Medicaid	−0.26	0.16	**−0.27**	−0.21	0.02	−0.18
		SES x COL x Medicaid	−0.22	0.27	−0.08	0.06	−0.22	−0.19
	SNP h^2	SES x COL	**−0.46**	**−0.53**	−0.05	−0.20	0.22	0.17
		SES x Medicaid	0.30	0.28	0.02	0.05	−0.30	−0.16
		SES x COL x Medicaid	0.32	0.27	0.01	0.20	−0.33	−0.26
	EA PGI	SES x COL	−0.14	−0.44	0.13	0.03	0.11	0.10
		SES x Medicaid	0.11	0.37	0.07	0.06	0.10	0.00
		SES x COL x Medicaid	0.09	**0.54**	−0.14	−0.13	−0.13	−0.11

N.B. The SES model includes SES as a fixed effect. The mean cash assistance model includes mean cash assistance as the state's economic policy and the Medicaid expansion model includes Medicaid expansion as the state's economic policy. For SES x COL, a more positive correlation coefficient suggests a stronger moderating effect by the state's cost of living. For SES x Medicaid and SES x COL x Medicaid, a more negative correlation coefficient suggests a stronger moderating effect by Medicaid expansion. All regression models exclude the EA PGI. Bolded values, significant at $p < 0.05$. * p values from spin permutation test (Supplemental Material). Socioeconomic status (SES). State's cost of living (COL). Medicaid (Medicaid expansion). Heritability (h^2). Single-nucleotide polymorphism (SNP). Educational attainment polygenic index (EA PGI).

regressions on SES and on the EA PGI for volumes and mean thicknesses, suggesting that greater SES-related differences also showed the strongest associations with educationally-relevant genetic variants. This result, while contrary to lay intuitions about a "nature versus nurture" dichotomy, is consistent with multiple lines of evidence showing that social and biological influences on child development are thoroughly intertwined (Nivard et al., 2024; Tucker-Drob and Harden, 2012). Heritability estimates, however, were generally not associated with SES-related brain differences, suggesting that the proportion of variance in a brain phenotype attributable to genetic differences across common variants (SNPs) or all variants (twins) does not covary with the magnitude of income-related disparities in those brain phenotypes.

Our findings related to heritability estimates generally comport with those from the literature. Our heritability estimates are congruent with previously reported heritability estimates in the ABCD study (Maes et al., 2023). As expected, we obtain higher heritability estimates from twin compared to genotype data and find that the difference between twin and SNP heritability estimates is greater for psychopathology than cognitive measures (e.g., Cheesman et al., 2017). We extend these findings to brain structure, as we find that the difference between twin and SNP heritability estimates in the brain are similar to the difference observed for intelligence measures.

We found that family SES was broadly associated with cognition and psychopathology, and with brain volumes and surface areas, whereas associations with mean thicknesses were sparser. Nearly all these SES associations were still observed after controlling for the EA PGI, but only a fraction were observed after controlling for global brain size. Moreover, SES-related differences in the adolescent brain were remarkably consistent across US states; there was significant geographical variation in SES associations in only a select number of brain volumes and surface areas. These moderated regions have previously been associated with SES (Farah, 2017; Rakesh and Whittle, 2021; Rosen et al., 2019; Yaple and Yu, 2020) and are typically involved in physiological regulation and sensory processing, such as the brainstem and thalamus (Monge Argilés et al., 2000) (Sherman, 2007), as well as higher-level functions related to memory and cognition (e.g., hippocampus volume, superior frontal surface areas, cerebral white matter volume) (Anand and Dhikav, 2012; du du du Boisgueheneuc et al., 2006; Stephens et al., 2020).

For some of these regions, the SES-brain association was greater in high- compared to low-cost-of-living states, and in some cases, this association was attenuated in states that expanded Medicaid. In contrast to a previous ABCD study (Weissman et al., 2023) that reported similar moderation effects for internalizing scores and hippocampal volume after adjusting for global brain size, we found that, for most SES-brain associations, moderation effects were substantially attenuated and no longer significant after adjusting for global brain size. However, unlike Weissman et al. (2023), who considered sample diversity by adjusting for the study site ethnicity, our analytic sample was, unfortunately, limited to participants of European ancestries, whose genotypes were most like individuals who participated in the previous large-scale EA GWAS. Therefore, we decreased our study's power to detect two- and three-way interactions and excluded many minoritized individuals who are disproportionately from lower socio-economic backgrounds and who might benefit most from social welfare policies. The exclusion of individuals and groups who do not have European genetic ancestries continues to be one of the most severe limitations of social science genomics research.

In line with previous studies (Judd et al., 2020; Kweon et al., 2022), SES and the EA PGI generally had additive associations across brain phenotypes. Even after adjusting for global brain size, several aspects of adolescent neurobiology were significantly associated with SES. These regions were related to memory consolidation, recollection, and integration (hippocampal volume and the parahippocampus, entorhinal, isthmus cingulate, and superior parietal surface areas) or are highly connected with these regions (amygdala, fusiform gyrus) (Anand and Dhikav, 2012; Nielsen et al., 2005; Takehara-Nishiuchi, 2014; J. Wang et al., 2014). Our findings are consistent with previous structural and functional studies that generally report smaller regions and less activation in memory-related regions of children from lower SES (Assari et al., 2020; Noble and Giebler, 2020; Rakesh and Whittle, 2021).

The present study is not without limitations. First, and most importantly, we cannot make causal claims about the effects of investigated policies on individual differences in brain structure given that other state-level factors may be driving the moderation associations. Generally, longitudinal designs, natural experiments, and randomized control trials are necessary to make causal claims on the effects of state-level economic context and policies (Gianicolo et al., 2020). Second, we focused on associations with the income-to-needs ratio, which is only one component of socioeconomic status. Future studies should investigate phenotypic associations with other facets of socioeconomic status, such as parental occupation or educational attainment, which may be differentially related to brain, cognition, and psychopathology during adolescence. Third, given that population-specific genetic variations and allele frequencies influence identified genetic associations, our analyses are not generalizable to individuals who do not have similar genotypes to the 1KG-EUR-like individuals included in this study. Our analyses were restricted to individuals of European ancestries due to insufficiently large EA GWAS results in samples from other genetic ancestries (Wang et al., 2022). Fourth, heritability estimates of brain phenotypes appear to vary across the lifespan: for instance, whereas heritability estimates of white matter tend to be constant from birth onwards, heritability estimates of cortical surface areas, thicknesses, and volumes increase between childhood and adulthood (Jansen et al., 2015; Lenroot et al., 2009). Therefore, correlations between heritability estimates and economic context may vary across the lifespan and should be further investigated. Finally, studies on developmental phenotypes other than brain structure are required to better understand the relationship between a phenotype's genetic associations and its responsiveness to the environmental context.

The present study contributes to a long-standing theoretical debate that has been of public interest but has received little empirical investigation. We show that the strength of genetic associations across brain regions is unrelated to their associations with macroeconomic contexts and policies in adolescents in the US. As both genetic factors, home contexts, and macroeconomic policies are concurrently associated with brain, cognition, and psychopathology in adolescents, integrative designs that jointly consider factors ranging from the genome to home to the legislature will be necessary to understand brain and psychological development during this critical period of the human lifespan.

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CRediT authorship contribution statement

K. Paige Harden: Writing – original draft, Supervision, Methodology, Funding acquisition, Conceptualization. **Katie Anne McLaughlin:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization. **Camille Michele Williams:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Conceptualization. **Travis Triplett Mallard:** Writing – review & editing, Visualization, Methodology, Formal analysis. **David G Weissman:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

The authors do not have permission to share data.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.dcn.2024.101455.

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