preferred for the ADHD symptoms of inattention and hyperactivity, and conduct problems, but not oppositional defiant behaviors. Direct genetic effects accounted for 11% to 24% of the variance, whereas indirect parental genetic effects accounted for 0% to 16% in ADHD symptoms and conduct problems. The correlation between direct and indirect genetic effects, or gene-environment correlations, decreased the variance with 16% and 13% for conduct and inattention problems, and increased the variance with 6% for hyperactivity problems. The current study provides empirical support for that parents both matter and make a difference for the development of childhood externalizing behaviors. The parental contribution to decrease in variation of inattention and conduct problems by gene-environment correlations would limit the number of children reaching clinical ranges in symptoms. Not accounting for indirect parental genetic effects can lead to both positive and negative bias when identifying genetic variants for childhood externalizing behaviors.

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## Impact of Substance Use Polygenic Risk Scores on Substance-Naive Brain Structure in Adolescence

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*Keywords*: Brain structure, Adolescence, Addiction, GWAS, Genetics

Genetic factors explain 40–60% of the population variability in developing alcohol or nicotine addiction. Longitudinal studies and mega-analysis of MRI-derived brain phenotypes show associations between alcohol and tobacco use and brain structure. While still unclear, emerging data indicate that these brain structure correlates may, at least partially, reflect genetically conferred predisposing risk factors for alcohol and drug involvement. The goal of this project is to evaluate whether there is evidence for a common genetic vulnerability to both substance use and brain development. Brain-imaging data and genetic data for 6143 adolescents of European-ancestry in ABCD were used to assess whether polygenic risk scores(PRS) based on adult substance-use predict brain structure in ABCD intake-assessments, prior to drug-use. PRS were calculated for five substance use phenotypes (drinks per week, cigarettes per day, age of initiation, smoking cessation and smoking initiation) based on genomic loci identified by GSCAN GWAS meta-analysis. Associations between PRS and 142 brain structure phenotypes, particularly cortical thickness, and surface area, are estimated using mixed-effects models. Standardized effects across all comparisons (5 PRS $\times$ 142 brain structure phenotypes) ranged from $-$ 0.040 to 0.037. The average effect across 142 brain structures was $-$ 0.005 for age of initiation of smoking, 0.006 for cigarettes per day, 0.003 for drinks per week, and 0.003 for smoking cessation. While average direction of effect suggests PRS risk for smoking and alcohol use were associated with larger brain structures, no individual effects were significant after correcting for 142 independent tests.

## Polygenic Effects on Individual Rule Breaking and Peer Rule Breaking in Pathways to Alcohol Sips in the ABCD Study

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*Keywords*: Polygenic, Alcohol, Rule Breaking, Peers, Early Adolescence

Genetic influences and gene-environment correlations (rGE) can underlie risky individual and peer behavior during adolescence, increasing risk for later substance use. Less research has examined this in early adolescence. We examined a cross-time cross-lag model using data from the Adolescent Brain Cognitive Development (ABCD) study at wave 2 (Mage = 11.55) and 3 (Mage = 12.42). Polygenic scores for risky behavior (PGS; Linnér et al., 2019) were predictors of individual and peer rule breaking (RB) at wave 2 and 3, with PGS and wave 3 constructs predicting past-year alcohol sips at wave 3. This was examined separately across European American (n = 6180), African American (n = 1784), and Latinx (n = 2411) subgroups covarying for age, gender, site, income, and genetic principal components. In European Americans, there was stability in individual (B = 0.64, $p < 0.001$) and peer (B = 0.38, $p < 0.001$) RB and correlations within wave 2 and 3 (r = 0.15, $p < 0.001$; r = 0.13, $p < 0.001$). At wave 2 and 3, the PGS predicted individual (B = 0.09, $p < 0.001$; B = 0.03, p = 0.02) and peer (B = 0.08, $p < 0.001$; B = 0.06, $p < 0.001$) RB, and alcohol sips at wave 3 (B = 0.04, p = 0.02). Individual RB predicted peer RB from wave 2 to 3 (B = 0.09, $p < 0.001$), and vice-versa (B = 0.06, $p < 0.001$). Peer RB at wave 3 was associated with alcohol sips at wave 3 (B = 0.14, $p < 0.001$), but individual RB was not. Associations in African American and Latinx subgroups were largely absent. Results indicate individual and peer RB influence one another within and across time with active/evocative rGE likely implicated. As a result, peer RB can contribute to alcohol sips in early adolescence.

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## Are Education/Mortality Disparities Widening in Countries Other Than the US?: Twin-Differenced Models of Age and Cohort in IGEMS.

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*Keywords*: Education, Mortality, Disparities, Twins

Education is known to have a graded relationship with morbidity and mortality globally. The education/mortality gradient has been growing steeper as income inequality and educational disparities have been growing in the United States. However, much less is known about temporal trends in this relationship in more equitable countries with larger safety nets and lower levels of income inequality. Further, prior estimates of the educational gradient may be biased by family background and genetic effects that have been ignored in most population-based analyses. Our analysis seeks to explore temporal changes in the education/mortality gradient in countries other than the United States (Sweden, Australia, and Finland) using several harmonized cohorts of twins in the Consortium on Interplay of Genes and Environment across Multiple Studies (IGEMS). Findings show that while education/mortality gradients are largely robust to inclusion of controls for both family background and genetics, there is no evidence that these gradients are growing steeper in Sweden, Australia, and Finland, but rather, remain consistent across a wide range of historical birth cohorts.

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## Genetic Architecture of Self-rated Health: Relationship with Physical Health, Cognition Function, and Depression

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*Keywords*: Self-rated health, Depression, Cognition, Physical health, Age differences

The fact that self-rated health (SRH) predicts mortality and a variety of other health outcomes independent of objective health measures generates questions about mechanisms and etiologies. SRH can be considered an indicator of physical health, per se, resulting from active cognitive processing of explicit information about one's own health and intuitive knowledge of symptoms and physical sensations. The extent to which SRH taps shared cultural ideas about health should be reflected in estimates of the shared environmental component of variance (C). SRH has also been associated with emotional health measures, such as neuroticism and depression. Previous analyses have been limited by sex (only women), sample size, age (range = 63–76), and failure to include cognitive function (Leinonen et al., 2005). The current analysis used data from 10,682 adults ranging in age from 22 to 102 from the international Interplay of Genes and Environment Across Multiple Studies (IGEMS) consortium to investigate the genetic architecture of SRH. Independent pathways model of SRH included CIRS (Cumulative Illness Rating Scale), MMSE (Mini-Mental Status Exam), and depression (CES-D or CAMDEX), with age, sex, and country included as covariates. All genetic variance for SRH was shared with CIRS, MMSE, and depression. Comparison of groups older and younger than 74 indicated age differences in genetic architecture of SRH. Evidence suggests that the discordance between objective and subjective health increases in late adulthood, possibly as a result of greater emphasis on psychological rather than physical components of subjective health assessments by older adults.

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## Adjusting for Genetic Confounding Using Polygenic Scores Within Structural Equation Models

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*Keywords*: Genetic confounding, Polygenic scores, Structural equation models

Associations between exposures and outcomes in observational research are prone to unobserved confounding, including arising from genetic effects on exposures and outcomes. Researchers have started adjusting for genetic confounding using polygenic scores. However, adjustment using polygenic scores can be insufficient due to measurement error. Here we build on previous work (Pingault et al., 2021) combining measured genetic variants and heritability estimates from twin- and genome-wide association studies using structural equation modelling (SEM). We developed a method that enables adjustment for genetic confounding in the association between multiple continuous exposures and an outcome of interest. Our method is implemented in R software, allowing raw data and covariance matrices as input and a range of estimators including bootstrapping for indirect effects. We provide estimates for genetic confounding, genetic overlap, and environmentally mediated genetic effects. Simulations using both simulated polygenic scores and SNP data show that our method accurately captures genetic confounding in the exposure-outcome associations. We show that estimated quantities are largely unbiased even under model misspecification, e.g. residual correlation between exposures. Under misspecifications however, environmentally mediated genetic effects should be interpreted carefully. The nature of SEM will enable further extensions to non-continuous data and other models.

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