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# Educational Attainment Polygenic Score Predicts Inhibitory Control and Academic Skills in Early and Middle Childhood

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## Abstract

Inhibitory control skills are important for academic outcomes across childhood, but it is unknown whether inhibitory control is implicated in the association between genetic variation and academic performance. This study examined the relation between a GWAS-based (EduYears) polygenic score indexing educational attainment (EA PGS) and inhibitory control in early ($M_{age}$ = 3.80 years) and middle childhood ($M_{age}$ = 9.18 years), and whether inhibitory control in early childhood mediated the relation between EA PGS and academic skills. The sample comprised 731 low-income and racially/ethnically diverse children and their families from the longitudinal Early Steps Multisite study. EA PGS predicted middle childhood inhibitory control (estimate = 0.09, *SE* = .05, $p < .05$) and academic skills (estimate = 0.18, *SE* = .05, $p < .01$) but did not predict early childhood inhibitory control (estimate = 0.08, *SE* = .05, $p = .11$); thus, mediation was not tested. Sensitivity analyses revealed that effect sizes were similar across European and African American groups. This study suggests that inhibitory control could serve as a potential mechanism linking genetic differences to educational outcomes.

### Keywords

educational attainment; polygenic score; inhibitory control; academic skills; longitudinal

Achieving higher education is associated with better health outcomes and increased life satisfaction[1,2]. In hopes to improve educational outcomes for all, researchers have made great strides in uncovering the genetic architecture underlying educational attainment, conducting several large-scale genome wide association studies (GWAS) analyzing the extent to which millions of genetic variants are associated with the number of years of education one achieves[3–5]. GWAS findings can be used to compute a polygenic score, calculated by weighting each individual's trait-associated alleles by effect size

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and summing across the variants[6]. Several recent studies have considered an educational attainment polygenic score (EA PGS), consistently demonstrating the score's predictive utility across multiple outcomes, with several examining the score in children[7–10]. Although the association between educational attainment polygenic scores and children's academic outcomes has been established, more research is needed to examine potential childhood mechanisms linking genetic differences to educational attainment to better understand the developmental process and targets of future intervention. This study examined whether child inhibitory control mediates the association between a polygenic score of educational attainment and academic performance in a low-income and racially/ethnically diverse sample of children studied prospectively from ages 2 to 10.5 in the United States.

## Linking Genes to Achievement

The GWAS representing educational attainment[3–5] has quickly led to a burgeoning literature demonstrating the predictive validity of a polygenic score of educational attainment[11]. For example, using a sibling-design that controls for population stratification and family-level environmental factors, a study of US adults found that the sibling with a higher EA PGS went on to obtain more schooling than their sibling with a lower EA PGS[12]. More specifically, each standard deviation increase in polygenic score was associated with an additional one third of one year of completed schooling, a moderate effect size. In addition to predicting educational attainment in adults, research has also shown the predictive ability of EA PGS on other academic and cognitive measures. Studies conducted in the UK have found that an EA PGS predicted teacher-rated achievement at ages 7, 12, and 16 (3%, 5%, and 9% of the variance, respectively), and 3% of the variance in academic motivation measured at age 16[13,14]. In an adult sample, an EA PGS predicted performance on cognitive measures of verbal and spatial reasoning (4% and 2.7% of the variance, respectively)[15]. In sum, these studies demonstrate that polygenic scores of educational attainment predict educational outcomes from childhood that can continue through adulthood.

It is likely that there are multiple factors that explain the relation between a polygenic score and educational attainment. In fact, researchers are urged to focus efforts on identifying intermediate phenotypes that mediate associations between genes and outcomes to elucidate the developmental process (i.e., phenotypic annotation)[16]. Recent work has linked EA PGS with *non-cognitive skills*[17]. For example, an EA PGS accounted for between 8% and 16% of the relation between personality domains and educational achievement in a sample of 16-year-olds assessed at the end of compulsory education in the UK[14]. Others have posited that symptoms related to ADHD could be a potential intermediate phenotype. In a sample of 12-year-old children in the Netherlands, an EA PGS predicted outcomes related to ADHD (i.e., attentional problems, impulsivity) and educational achievement, suggesting that self-regulatory behaviors could mediate the link between genes and educational attainment[9]. In the large-scale longitudinal Dunedin, New Zealand study, children with a higher EA PGS had fewer symptoms of ADHD (i.e., impulsive aggression, hyperactivity, lack of persistence, inattention, and impulsivity), measured from 3 to 11 years using a combination of observational tasks and parent and teacher reports[8]. With the same sample, individuals with a higher EA PGS demonstrated warmer, sensitive, and stimulating parenting as adults, and this was through greater cognitive ability and higher self-control assessed in middle and

late childhood[18]. Together, this research is beginning to suggest that polygenic influences on educational attainment operate through childhood self-regulation[8].

There is a need for replication and generalization of GWAS-derived polygenic scores across diverse groups, as nearly 70% of GWASs of educational attainment have been drawn primarily from samples of European-descent[12,19]. Current polygenic scores, formed from GWAS of individuals of European ancestry, may be less predictive when applied to admixed samples based on artifacts of ancestry[20–22], sample differences (e.g., age, cohort), and importantly, differences in environment (e.g., systemic racism). For individuals of African ancestry, a polygenic score based on a large-scale GWAS of educational attainment accounted for less variance in the number of years of schooling (1.6%) compared to individuals of European ancestry (11–13%)[3], with another study also finding attenuated prediction in individuals with African heritage[23]. However, until there is increased representation in human genetic research[24], scientific discoveries will continue to benefit European populations, exacerbating health disparities[20]. As such, it is of paramount importance to close the representation gap in genetic research by conducting discovery GWAS and developing appropriate polygenic scores for multiple global populations. However, the time and resources required to gather these data raise the question of whether it is preferable, in the meantime, to exclude individuals of non-European ancestry from most of the research using polygenic scores until more appropriate data and methodology are available, or to accept the pitfalls of conducting this research with available data.

There are reasons to be cautious about applying current polygenic scores formed from GWAS of individuals of European ancestry to samples of non-European ancestry. Allele frequencies and patterns of linkage disequilibrium differ across populations, raising the potential for false positive genetic associations if this *population stratification* is not properly controlled for. Further, findings relying on GWAS of individuals of European ancestry likely overlook variants important for an outcome among other groups. Observed differences in genetic associations or the distribution of polygenic scores across ancestry groups can be due to artifacts caused both by unattributed population stratification and by bias in methods such as genotyping (e.g., selection of tag SNPs) and imputation (e.g., linkage disequilibrium structure)[22]. Consequently, it is imperative to note that such findings are not and should never be taken as evidence of innate genetic differences between ancestry groups in susceptibility to an outcome. Bearing this in mind, we argue that the benefits of including individuals of non-European ancestry in current research using available data are enough to outweigh the drawbacks, and that there is still much to gain by utilizing current polygenic scores in non-majority samples, provided conclusions are taken with an appropriate amount of caution.

For example, one longitudinal study of African American children found that an educational attainment polygenic score predicted 1.4% of the variance in early childhood math achievement and higher odds of obtaining post-secondary education[25]. In a follow-up of the same African American sample, the association between the educational attainment score and years of education was mediated by academic achievement in adolescence[26]. Together, these findings suggest the predictive ability of educational attainment polygenic scores in African American samples and elucidates potential developmental pathways that

link polygenic propensity for educational attainment and academic outcomes for African American youth.

## Inhibitory Control as a Potential Mechanism

Inhibitory control, a dimension of temperament, is defined as the ability to willfully control potentially interfering thoughts and behaviors in the service of reaching long-term goals[27,28]. Inhibitory control emerges in toddlerhood and develops rapidly into early childhood [27,29,30], making it a key period to study, particularly as children enter preschool and grade school. Inhibitory control behaviors underlie children's academic skills, with a vast body of literature demonstrating the link between inhibitory control and academic outcomes[31]. For example, inhibitory control was associated with math and literary skills in early childhood, and predicted grade point average and school absences in middle to late childhood[32–34]. It is possible that inhibitory control could link educational attainment genetic variation and achievement.

It has been theorized that the executive attention system is a potential mechanism explaining the relation between inhibitory control and academic performance, as this system allows children to increasingly develop voluntary control over their own thoughts and behavior[35,36]. This system develops as children enter formal schooling, thus aiding in their ability to orient toward learning activities[31]. Inhibitory control also contributes to adaptive emotional regulation, which in turn, facilitates positive teacher-child interactions and promotes school liking and engagement[37,38]. As inhibitory control behaviors are implicated across various cognitive and educational outcomes, it is possible that a proportion of the variance in inhibitory control can be accounted for by genetic variation associated with educational attainment.

Generally, twin studies support temperament theories that posit a biological basis to inhibitory control, with additive genetics consistently explaining variability in inhibitory control throughout early to late childhood[39–41]. In addition, intervention studies have also demonstrated that inhibitory control is environmentally malleable. The Family Check-Up, a brief intervention centered on improving parenting practices through motivational interviewing techniques, has been shown to improve inhibitory control and effortful control in childhood in the current sample. For example, one study found that the Family Check-Up indirectly improved children's effortful control throughout early childhood by improving proactive parenting[42]. Additionally, the Family Check-Up indirectly promoted children's inhibitory control and language development at age 3 to 4 through increases in positive parenting one year prior[43]. In later childhood, the Family Check-Up was indirectly associated with reduced risk of internalizing and externalizing behaviors in adolescence by promoting inhibitory control in middle childhood[44]. The current research provides evidence that inhibitory control is an important and malleable intermediate phenotype linking genes to educational attainment. Elucidating the mechanisms linking genetic differences to educational outcomes can help us better understand how to provide educational success to all students[11,45].

## Current Study

The first goal of this study was to test a GWAS-based polygenic score indexing educational attainment (EA PGS) as a predictor of 1) inhibitory control in early and middle childhood and 2) academic skills in middle childhood in a low-income and racially/ethnically diverse sample of children. It was hypothesized that EA PGS would positively predict higher levels of inhibitory control and academic skills[8,9]. Another aim was to test whether inhibitory control in early childhood mediated the relation between EA PGS and academic skills. We hypothesized that there would be significant mediation, such that inhibitory control would partially account for the association between EA PGS and academic skills[8].

## Material and Methods

### Participants

The study comprised 731 racially/ethnically diverse, low-income families with 2-year-old children recruited from Women, Infants, and Children Nutritional Supplement Programs (WIC) in three distinct US communities between 2002 and 2003: Eugene, Oregon (suburban), Charlottesville, Virginia (rural), and Pittsburgh, Pennsylvania (urban). One child was tracked per family. Families of toddlers at risk for conduct problems were recruited through screening procedures, defined as 1 *SD* above the mean on at least two of the following measures: (a) sociodemographic risk: less than or equal to a mean of 2 years of post-high school education between parents and low family income using WIC criterion; (b) primary caregiver risk: maternal depression, daily parenting challenges, self-report of substance use or mental health diagnosis, or adolescent parent at birth of first child; and (c) toddler problem behaviors or high-conflict relationships with adults. Primary caregivers (97% mothers) reported on their race/ethnicity: 46.8% European American, 32.6% African American, 7.3% Latino/Hispanic, .6% Native American, 12.7% biracial or other. Almost a quarter of primary caregivers had less than a high school education, 41% had a high school diploma or general education diploma (GED), and 32% had 1–2 years of post-high school education. More than two-thirds of families reported an annual income of less than $20,000 (see Dishion et al., 2008 for additional study and sample information).

All waves of the study were approved by a University Institutional Review Board and all participants provided written informed consent (or assent prior to the age of 18). After the baseline assessment at age 2, families were randomly assigned to a control or intervention condition. Families in the control condition received WIC services as usual. Participants in the intervention group were offered the Family Check-Up. The Family Check-Up intervention consists of three sessions: assessment, initial interview, and feedback[46]. Families were followed-up when children were 3, 4, 5, 7.5, 8.5, 9.5, and 10.5 years old for assessments in the home, and families in the intervention condition were also offered the Family Check-Up services through child age 10.5. As intervention effects on child inhibitory control have previously been reported[42–44], intervention status was treated as a covariate in the current report.

## Procedure

Primary caregivers completed questionnaires regarding their children's inhibitory control behaviors at child ages 2, 3, 4, 5, 7.5, 8.5, 9.5, and 10.5. At the 7.5- and 8.5-year home visits, the Woodcock-Johnson III Tests of Achievement were administered.

Participants provided saliva samples at the age 14 home visit with Oragene kits for genotyping. DNA was extracted and normalized at RUCDR Infinite Biologics at Rutgers University, and samples were genotyped using the Affymetrix Axiom Biobank 1 Array. Any SNP or individual with a missing data rate greater than or equal to 5% was removed (no participants met this criteria), and any SNP with a minor allele frequency less than 1% was removed. Additionally, SNPs not in Hardy-Weinberg equilibrium at $p < 10^{-6}$ were removed.

## Measures

**Educational Attainment Polygenic Score.—**Polygenic scores were formed based on a sample size-weighted meta-analysis of GWAS studies across 71 cohorts ($N$ = 1,131,881) including individuals > 30 years of age of European ancestry from the US (e.g., Add Health; Wisconsin Longitudinal Study), the UK (e.g., the UK Biobank), Australia, and across Europe (e.g., Finland, Germany, Croatia, Greece) that asked participants the number of years of education they completed [3]. We formed effect weighted polygenic scores using imputed data. Single nucleotide polymorphisms (SNPs) were screened from our data based on the following criteria: missing SNP or individual data > 5%, MAF < .01%, SNPs departing from HWE at a $p$ threshold of .000001, SNPs within the Major Histocompatibility Complex, and synonymous SNPs. PLINK's clumping procedure was used to account for non-independence, which groups SNPs based on linkage disequilibrium (LD) and selects one based on the $p$ value in the summary statistic file. Polygenic scores (EA PGS) were formed based on $p$ thresholds of .001, .01, .05, and .10, with each score being a ratio of 'risk' alleles (weighted by effect size) divided by total alleles. We chose to use the pruning and thresholding method rather than those that rely on inclusion of all SNPs weighted by effect size because the inclusion of all available variants can heighten differences in the distributions of polygenic scores across ancestry groups, increase correlations between polygenic scores and ancestry principal components, and exacerbate the problem of uncontrolled population stratification[47,48].

**Genetic ancestry.—**To account for systematic genetic variation due to ancestry, regions of long-range LD were screened out and local LD were pruned using PLINK's sliding window procedure (thresholds of $r^2$ = .20, window size = 200 SNPs, step size = 100 SNPs). Then principal components analysis was performed on non-imputed genetic data using PLINK 1.9.21 (www.cog-genomics.org/plink/1.9/), and the first 20 principal components (PCs) were extracted[49]. The effects of all 20 PCs on EA PGS were regressed out prior to analyses, and residuals were used in analyses. Higher scores on the first genetic ancestry principal component were associated with African American ancestry and higher scores on the second ancestry principal component were associated with Latinx and Native American ancestry.

**Inhibitory control.—**Two measures were used to assess children's inhibitory control. First was the 13-item inhibitory control scale of the Children's Behavior Questionnaire[50] that was administered to caregivers longitudinally at ages 2, 3, 4, 5, and 7.5. Each item was rated on a 7-point Likert scale ranging from 1 (*extremely untrue of child*) to 7 (*extremely true of child*) over the last six months. Sample items include "*My child has difficulty waiting in line for something*" and "*My child has a hard time following instructions.*" In our study, Cronbach's alpha ranged from .65 to .83. This measure demonstrated adequate reliability and validity[50].

The second was the 8-item inhibitory control scale of the Temperament in Middle Childhood Questionnaire[51] that was administered to caregivers longitudinally at ages 8.5, 9.5, and 10.5 as an upward extension of the Children's Behavior Questionnaire. Caregivers rated each item on a 5-point Likert scale ranging from 1 (*almost always untrue of your child*) to 5 (*almost always true of your child*). Example items include "*My child has a hard time stopping him/herself when told to do so*" and "*My child likes to plan carefully before doing something.*" Cronbach's alpha ranged from .64 to .71 in our study. The inhibitory scale has demonstrated construct validity[51].

Unconditional confirmatory factor analyses were conducted to form general factors that represented inhibitory control across early childhood (ages 2, 3, 4, and 5) and middle childhood (ages 7.5, 8.5, 9.5, and 10.5).

**Academic skills.—**The Letter-Word Identification, Calculation, and Spelling subtests of the Woodcock-Johnson III Tests of Achievement[52] were administered by trained research staff in the home longitudinally at 7.5 and 8.5 years of age. The Letter-Word Identification subtest assess children's ability to identify letters and words, as items increase in difficulty. The Calculation subtest asks children to write single numbers and perform mathematical procedures including addition and subtraction. Finally, the Spelling subtest assesses children's pre-writing skills including drawing lines, tracing numbers, writing uppercase and lowercase letters, and spelling orally presented words. Standard scores were formed based on a mean of 100 and a standard deviation of 15. A mean composite of scores from 7.5 and 8.5 years was formed.

**Covariates.—**Covariates included gender (0 = *male*, 1 = *female*; $M = .50$, $SD = .50$), a standardized score representing family monthly income across ages 2 – 10.5 ($M = 5.06$, $SD = 1.88$), study site location (Eugene and Charlottesville compared to Pittsburgh indexed with two dummy codes), and intervention status (0 = *control*, 1 = *intervention*).

## Statistical Approach

All analyses were conducted using Mplus version 7.4[53]. First, descriptive statistics and zero order correlations were conducted. Confirmatory factor analyses were modeled with inhibitory control at ages 2, 3, 4, and 5 to index inhibitory control across early childhood, and ages 7.5, 8.5, 9.5, and 10.5 to index inhibitory control across middle childhood. After regressing out effects of all 20 PCs on EA PGS, residual scores were Z-scored. SES was mean centered prior to running models. Initial models included the main effect of covariates (gender, SES, study site, and intervention status), two-way interactions between polygenic score and covariates[54], and the main effect of the polygenic score. Main effects of all

covariates were retained in the final models, regardless of significance, but nonsignificant two-way interactions between the polygenic score and covariates were not included.

Initial regression models were tested examining the association between the polygenic score with latent inhibitory control in early and middle childhood, and with academic skills. Mediation models were then conducted if the mediator was significantly associated with the predictor and outcome (Figure 1). The *a* path refers to the relation between the polygenic score and inhibitory control in early childhood, the *b* path refers to the association between inhibitory control in early childhood and academic skills, and the *c* path represents the relation between EA PGS and academic skills. Mediation was determined by a significant indirect path between *a* and *b* paths. Full information maximum likelihood (FIML) estimation was used with all analyses to handle missing data.

## Results

### Preliminary analyses.

Descriptive statistics and zero-order correlations are presented in Table 1 and 2, respectively, and were computed using Mplus version 7.4[53] with FIML. All variables were normally distributed and were within acceptable ranges for skewness and kurtosis[55].

EA PGS scores across all thresholds were highly intercorrelated. The $p = .05$ score was selected to represent EA PGS with hypothesis testing to reduce the number of models fit and control type 1 statistical error. EA PGS was generally unrelated to early inhibitory control, weakly correlated with inhibitory control in middle childhood, and modestly correlated with overall academic skills. Additionally, EA PGS was unrelated to study site, intervention status, and gender, but was positively correlated with SES. Inhibitory control was consistently correlated across age and females had higher scores on inhibitory control across all ages ($r$ ranging from .09 to .15, $p < .05$). Intervention was weakly positively correlated with inhibitory control at age 10.5 and negatively correlated with overall academic skills[56]. PC1, the first genetic ancestry principal component associated with African American ancestry, was uncorrelated with the outcome variables (not included in Table 2). However, PC2 and PC10 were significantly correlated with early inhibitory control (PC2: $r = -.15$, $p<.01$; PC10: $r = -.14$, $p<.01$) and late childhood inhibitory control (PC2: $r = -.12$, $p<.05$; PC10: $r = -.10$, $p<.05$), and PC6 and PC11 were correlated with academic skills (PC6: $r = .14$, $p<.05$; PC11: $r = -.11$, $p<.05$).

An unconditional CFA of inhibitory control in early childhood (ages 2, 3, 4, and 5) in the full sample showed adequate model fit ($\chi^2(2) = 33.32$, $p < .001$; SRMR = .033; RMSEA = .147; CFI = .959), and standardized loadings were consistently high across age, except for inhibitory control at age 2, where loadings ranged from moderate to high (.58–.76). An unconditional CFA of inhibitory control in middle childhood (ages 7.5, 8.5, 9.5, and 10.5) in the full sample showed good model fit ($\chi^2(2) = 3.817$, $p = .148$; SRMR = .010; RMSEA = .038; CFI = .998), and standardized loadings were consistently high across age (.73–.79).

### Multivariate models predicting latent inhibitory control and mean academic skills from polygenic score.

Regression models examining the relation between EA PGS and inhibitory control and overall academic skills are presented in Table 3. For the early childhood inhibitory control model, all two-way interactions between EA PGS and covariates were nonsignificant. EA PGS was not significantly associated with inhibitory control in early childhood (estimate = 0.08, *SE* = .05, *p* = .11, 0.6% of the variance). Thus, without temporal precedence, mediation models were not tested. EA PGS was associated with inhibitory control in middle childhood (estimate = 0.09, *SE* = .05, *p* < .05, 0.9% of the variance) and with overall academic skills (estimate = 0.18, *SE* = .05, *p* < .01, 3.0% of the variance).

### Sensitivity Analysis.

Although there was not enough statistical power to run models separately, effect sizes were similar across European American and African American groups for early childhood inhibitory control (European Americans: estimate = 0.11, *SE* = .07, *p* = .11; African Americans: estimate = −0.05, *SE* = .09, *p* = .56), middle childhood inhibitory control (European Americans: estimate = 0.05, *SE* = .07, *p* = .43; African Americans: estimate = 0.08, S*E* = .09, p = .37) and academic skills (European Americans: estimate = 0.13, *SE* = .07, *p* < .05; African Americans: estimate = 0.21, *SE* = .09, *p* < .05).

Additionally, the same pattern of results was found when analyses were conducted with only the control group, such that EA PGS was not associated with early childhood inhibitory control, positively associated with middle childhood inhibitory control (estimate = 0.13, *SE* = .07, *p* < .05), and positively related to academic skills (estimate = 0.18, *SE* = .07, *p* < .01).

## Discussion

In a low-income and racially/ethnically diverse sample of children, we examined the extent to which a polygenic score indexing educational attainment (EA PGS) predicted inhibitory control in early and middle childhood and academic skills in middle childhood. Another aim of the study was to test whether the association between EA PGS and academic skills was mediated by inhibitory control in early childhood. Overall, we found that EA PGS was associated with inhibitory control and predicted overall academic skills in middle childhood. However, EA PGS was not predictive of inhibitory control in early childhood, thus mediation was not tested. Sensitivity analyses suggested that effect sizes were comparable across racial/ethnic groups. Our study expands on the predictive validity of polygenic scores and provides preliminary evidence that genetic variation indexing educational attainment was also related to inhibitory control and academic skills in middle childhood.

First, our study demonstrated that an EA PGS was associated with inhibitory control in middle, but not early, childhood. We hypothesized that the polygenic score would be positively associated with inhibitory control in early childhood, partially accounting for the relation between EA PGS and academic skills. As EA PGS was not associated with early childhood inhibitory control, the findings suggest that early self-regulatory skills are not involved in the pathway from genes identified from the EduYears GWAS[3] to later

academic outcomes. However, it is also possible that the use of a non-matched sample (low-income, racially/ethnically diverse) contributed to attenuated prediction of EA PGS with early childhood inhibitory control in our study, as there is some evidence to suggest that polygenic scores from GWASs of European individuals are less predictive when used in admixed samples[3,23]. Other research has demonstrated that childhood self-regulation, measured from ages 3 to 11, mediated the relation between an educational attainment polygenic score and later educational attainment[8]. At the same time, the executive attention system, a potential mechanism explaining the association between inhibitory control and academic performance, is thought to develop in middle childhood as children enter formal schooling and begin independently fostering peer relationships[31,37,38]. Thus, it is possible that inhibitory control may become more strongly implicated in the relation between genes and academic skills later in childhood. Additional research is needed to examine relations between EA PGS and components of self-regulation in early childhood.

Our findings are concordant with studies that examined other constructs related to self-regulation. More specifically, EA PGSs have been negatively associated with various ADHD behaviors including attentional problems, impulsivity, and hyperactivity[8,9], although at least one study of African American youth failed to find a predictive effect of the EA PGS on impulsivity in early or late adolescence[26]. In addition, we found that EA PGS accounted for 3% of the variance in overall academic skills. Our results, and specifically their magnitude (i.e., effect sizes), are comparable to studies of both matched and nonmatched samples that examined relations between EA PGS and academic outcomes across development, including mathematics performance, teacher-rated achievement, academic motivation, and cognitive assessments[13–15,25].

Another possibility is that genetic variation included in EA PGS could be exercising a pleiotropic effect on inhibitory control and academic skills, where genetic variation is implicated across multiple biological pathways or one biological pathway has effects on multiple outcomes[57]. Although this model has not been tested using PGS, researchers using quantitative genetic methods found that a shared genetic factor accounted for the association between various measures of self-regulation and academic outcomes[58,59].

Genetic influences are not deterministic, as many children with a low EA PGS perform well academically. Instead, associations between PGS and outcomes of interest reflect complex transactions between genes and the environment[60]. In fact, recent work has shown the importance of the rearing environment in explaining associations between genetic variation and children's academic outcomes[18,61,62], and an EA PGS was less predictive of postsecondary education and college completion for individuals with lower school-level socioeconomic status[63]. Together, this study and other recent research contributes to our understanding of the various pathways that link genetic variation to academic outcomes. However, failure to also consider the role of the environment can perpetuate the misappropriation of genetic research to support the superiority/inferiority of human groups[64]."

### Strengths and Limitations

Our study had several methodological strengths, including the creation of our polygenic score, as alleles with larger effect sizes are more likely to generalize across diverse samples[49,65,66]. Another strength was the inclusion of a racially/ethnically diverse sample, as the lack of diversity in genome-wide and polygenic approaches perpetuates a European-centric bias in genetic research[22] and limits our understanding of complex human traits[20]. While our study provides evidence that genetic variation associated with educational attainment is related to inhibitory control and academic skills in middle childhood, these findings should also be interpreted with caution. First, generalizability may be limited to children from families of low socioeconomic status and at high sociodemographic or family risk for conduct problems[46]. Another important limitation is that the PGS used in this study was derived from a GWAS of adults of European ancestry[3]. Research has suggested that current GWAS findings may not be fully representative of other racial/ethnic groups due to differences in linkage disequilibrium and allele frequencies[20,22,49], in addition to other sample differences (e.g., physical and sociocultural environments). Stratifying analyses by race/ethnicity is the standard and recommended procedure to control for potential confounding due to population stratification[12]; however, we were not powered to test our hypotheses separately by group. Sensitivity analyses revealed that effect sizes across European American and African American groups were of similar magnitude, with significant associations in the same direction as previous research[8,9], providing support that these are real associations. Yet, we acknowledge that processes linking genetic variation and outcomes could differ across genetic ancestry groups[60], making it imperative for researchers to develop approaches that better account for differences in linkage disequilibrium and allele frequencies[21] and for GWAS studies to include more diverse samples[20].

Utilizing a GWAS of individuals of European ancestry likely overlooks important variants in other groups and could reflect unmeasured environmental variables more common in one group, rather than actual genetic effects[12,67]. Researchers have suggested the possibility that ancestry principal components may partially account for genetic effects[47]. Of course, this study should not be taken as evidence for genetic differences across African American and European American ancestry on inhibitory control or academic skills, but rather highlights the need for GWAS to be more representative to make more accurate conclusions about the etiology of human traits and behavior[20,47].

## Conclusion

This study provides an introductory examination of inhibitory control as a potential mechanism linking genetic differences to educational outcomes. In addition, based on the score's predictive power across multiple outcomes, the findings suggest that the EA PGS represents broad genetic contributions to educational attainment. Future directions include utilizing GWAS with underrepresented samples and examining genetic associations with other measures of self-regulation in early and middle childhood. It would also be valuable for future research to consider other pathways through which genetic variation might be associated with educational attainment, such as physical health, so that we may best improve access to education for all individuals. Finally, another future direction includes considering

early prevention as a moderator of the effects of EA PGS on children's self-regulatory and academic outcomes. Examining the developmental processes associating genetic and environmental variability helps us better understand the etiology of academic skills.

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## Data Availability Statement:

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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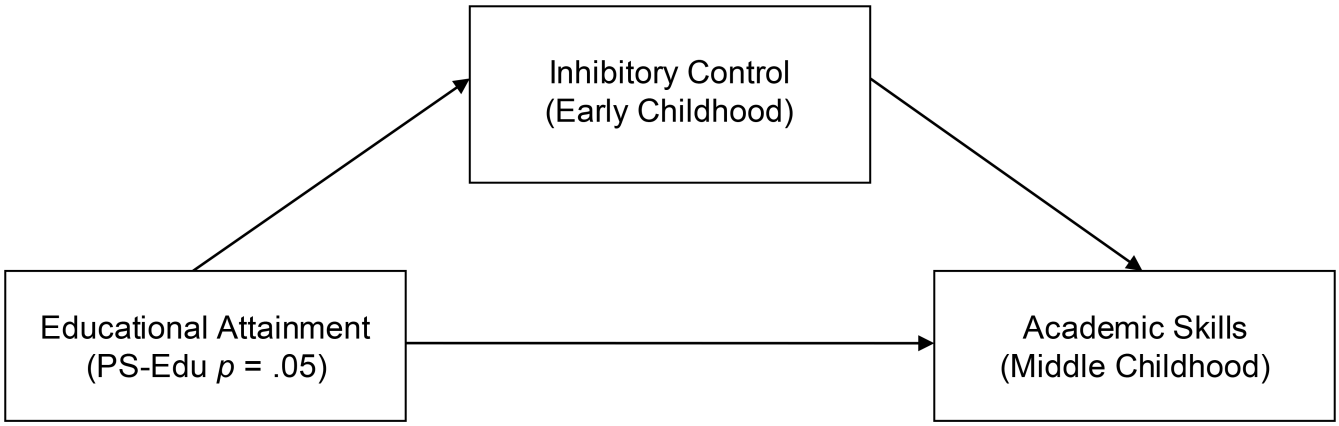


**Figure 1.**
Conceptual model of early childhood inhibitory control mediating the association between educational attainment polygenic score and academic skills in middle childhood

**Table 1.**

Descriptive statistics

| | *N* | Min | Max | Mean | SD | Skewness | Kurtosis |
|---|---|---|---|---|---|---|---|
| PS-Edu ($p$ = .001) | 515 | −3.16 | 3.97 | 0.00 | 1.00 | −0.02 | 0.42 |
| PS-Edu ($p$ = .01) | 515 | −2.95 | 3.00 | 0.00 | 1.00 | −0.42 | 0.20 |
| PS-Edu ($p$ = .05) | 515 | −3.25 | 2.74 | 0.00 | 1.00 | −0.23 | 0.23 |
| PS-Edu ($p$ = .10) | 515 | −3.47 | 2.80 | 0.00 | 1.00 | −0.25 | 0.28 |
| Inhibitory Control – Age 2 | 720 | 1.33 | 7.00 | 3.97 | 0.64 | −0.18 | 0.32 |
| Inhibitory Control – Age 3 | 658 | 1.46 | 6.62 | 4.24 | 0.61 | −0.13 | 0.39 |
| Inhibitory Control – Age 4 | 628 | 1.17 | 6.67 | 4.45 | 0.66 | −0.14 | 0.48 |
| Inhibitory Control – Age 5 | 616 | 1.80 | 7.00 | 4.67 | 0.74 | −0.32 | −0.17 |
| Inhibitory Control – Age 7.5 | 554 | 1.54 | 7.00 | 4.86 | 0.84 | −0.14 | −0.01 |
| Inhibitory Control – Age 8.5 | 548 | 1.50 | 4.88 | 3.27 | 0.32 | −0.37 | 0.06 |
| Inhibitory Control – Age 9.5 | 581 | 1.25 | 5.00 | 3.36 | 0.37 | 0.04 | 0.31 |
| Inhibitory Control – Age 10.5 | 564 | 1.63 | 5.00 | 3.45 | 0.39 | −0.06 | −0.24 |
| Overall academic skills | 446 | 47.00 | 127.50 | 99.23 | 12.44 | −0.49 | 0.81 |
| Site 1 | 731 | 0.00 | 1.00 | 0.37 | 0.48 | 0.54 | −1.72 |
| Site 2 | 731 | 0.00 | 1.00 | 0.26 | 0.44 | 1.11 | −0.76 |
| SES | 731 | 1.13 | 10.50 | 5.06 | 1.88 | 0.34 | −0.49 |
| Intervention | 731 | 0.00 | 1.00 | 0.50 | 0.50 | -- | -- |
| Gender | 731 | 0.00 | 1.00 | 0.50 | 0.50 | -- | -- |

*Note*. PS-Edu = polygenic score for educational attainment. Polygenic scores are calculated as proportion of educational attainment alleles below a particular $p$ threshold. Site 1 and Site 2 are Eugene and Charlottesville study site locations compared to Pittsburgh indexed with dummy codes, respectively. SES = socioeconomic status. Intervention is coded 0 = *control*, 1 = *intervention*. Gender is coded 0 = *male*, 1 = *female*.

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**Table 2.**

Zero-order correlations

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. PS-Edu ($p$ = .001) | - | | | | | | | | | | | | | | | | | |
| 2. PS-Edu ($p$ = .01) | .85** | - | | | | | | | | | | | | | | | | |
| 3. PS-Edu ($p$ = .05) | .75** | .88** | - | | | | | | | | | | | | | | | |
| 4. PS-Edu ($p$ = .10) | .70** | .82** | .94** | - | | | | | | | | | | | | | | |
| 5. IC – Age 2 | −.02 | .05 | .07 | .06 | - | | | | | | | | | | | | | |
| 6. IC – Age 3 | .01 | .07 | .09* | .07 | .52** | - | | | | | | | | | | | | |
| 7. IC – Age 4 | .01 | .05 | .04 | .03 | .41** | .53** | - | | | | | | | | | | | |
| 8. IC – Age 5 | −.04 | .04 | .05 | .04 | .38** | .54** | .61** | - | | | | | | | | | | |
| 9. IC – Age 7.5 | −.02 | .02 | .07 | .06 | .34** | .50** | .51** | .58** | - | | | | | | | | | |
| 10. IC – Age 8.5 | −.06 | .01 | .03 | .03 | .31** | .42** | .46** | .46** | .57** | - | | | | | | | | |
| 11. IC – Age 9.5 | .03 | .07 | .11* | .09* | .30** | .40** | .46** | .53** | .58** | .59** | - | | | | | | | |
| 12. IC – Age 10.5 | .02 | .10* | .13** | .12* | .25** | .39** | .43** | .44** | .53** | .57** | .62** | - | | | | | | |
| 13. Academic skills | .13** | .16** | .20** | .18** | .10* | .24** | .20** | .27** | .30** | .26** | .18** | .22** | - | | | | | |
| 14. Site 1 | −.01 | −.01 | −.01 | −.01 | −.05 | .04 | .06 | .12** | .08* | −.01 | .01 | .03 | −.09* | - | | | | |
| 15. Site 2 | −.01 | −.01 | −.01 | −.01 | .01 | .02 | .05 | .01 | .05 | .04 | .03 | .05 | .15** | −.45** | - | | | |
| 16. SES | .13* | .30** | .35** | .34** | −.01 | .08 | .10* | .12* | .09 | .06 | .08 | .12* | .21** | .09* | −.02 | - | | |
| 17. Intervention | −.02 | .01 | −.01 | −.02 | −.01 | .05 | .05 | .05 | .02 | .04 | .05 | .09* | −.09* | .01 | .01 | −.01 | - | |
| 18. Gender | −.01 | −.01 | −.01 | −.01 | .12** | .15** | .09* | .15** | .13** | .15** | .15** | .13** | .06 | .01 | −.01 | .01 | .01 | - |

*Note*. PS-Edu = polygenic score for educational attainment. Polygenic scores are calculated as proportion of educational attainment alleles below a particular $p$ threshold. IC = inhibitory control. Site 1 and Site 2 are Eugene and Charlottesville study site locations compared to Pittsburgh indexed with dummy codes, respectively. SES = socioeconomic status. Intervention is coded 0 = *control*, 1 = *intervention*. Gender is coded 0 = *male*, 1 = *female*.

* $p < .05$.

** $p < .01$

**Table 3.**

Polygenic score predicting inhibitory control and overall academic skills

| Early Childhood Inhibitory Control | | | | |
|---|---|---|---|---|
| | Est.(SE) | Lower CI | Upper CI | $R^2$ |
| Gender | **0.18(.04)** ** | 0.10 | 0.26 | 0.06 |
| Income | 0.10(.06) | −0.01 | 0.21 | |
| Site 1 | **0.10(.05)** * | 0.01 | 0.19 | |
| Site 2 | 0.09(.05) | −0.01 | 0.18 | |
| Group | 0.05(.04) | −0.03 | 0.13 | |
| PS-Edu $p = .05$ | 0.08(.05) | −0.02 | 0.17 | |
| **Middle Childhood Inhibitory Control** | | | | |
| | Est.(SE) | Lower CI | Upper CI | $R^2$ |
| Gender | **0.18(.04)** ** | 0.10 | 0.26 | 0.07 |
| Income | **0.11(.05)** * | 0.01 | 0.21 | |
| Site 1 | 0.07(.05) | −0.02 | 0.16 | |
| Site 2 | 0.08(.05) | −0.01 | 0.18 | |
| Group | 0.06(.04) | −0.02 | 0.14 | |
| PS-Edu $p = .05$ | **0.09(.05)** * | 0.01 | 0.19 | |
| **Overall Academic Skills** | | | | |
| | Est.(SE) | Lower CI | Upper CI | $R^2$ |
| Gender | 0.05(.05) | −0.04 | 0.14 | 0.11 |
| Income | **0.21(.05)** ** | 0.12 | 0.31 | |
| Site 1 | −0.04(.05) | −0.14 | 0.06 | |
| Site 2 | **0.13(.05)** * | 0.03 | 0.23 | |
| Group | −0.09(.05) | −0.17 | 0.01 | |
| PS-Edu $p = .05$ | **0.18(.05)** ** | 0.09 | 0.27 | |

*Note*. Est. = standardized partial regression coefficient estimate. *SE* = robust standard error. CI = confidence interval. PS-Edu = polygenic score for educational attainment. Gender is coded 0 = *male*, 1 = *female*. Site 1 and Site 2 are Eugene and Charlottesville study site locations compared to Pittsburgh indexed with dummy codes, respectively. Intervention is coded 0 = *control*, 1 = *intervention*.

* $p < .05$

** $p < .01$.