Disentangling the influences of parental genetics on offspring's cognition, education, and psychopathology via genetic and phenotypic pathways

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ABSTRACT

Background: Specific pathways of intergenerational transmission of behavioral traits remain unclear. Here we aim to investigate pathways by which parental genetics can impact offspring cognition, educational attainment and psychopathology in youth.

Methods: Participants for the discovery sample were 2189 offspring (aged 6-14 years), 1898 mothers and 1017 fathers who underwent genotyping, psychiatric and cognitive assessments. We calculated polygenic scores (PGS) for cognition, educational attainment, attention-deficit hyperactivity disorder (ADHD), and schizophrenia for the trios. Phenotypes studied included educational outcomes, cognitive measures, ADHD and psychotic symptoms. We used a stepwise approach and multiple mediation models to analyze the effect of parental PGS on offspring behavior via offspring PGS and parental phenotype. Significant results were replicated in a sample of 1029 adolescents, 363 mothers and 307 fathers.

Results: Maternal and paternal PGS for cognition influenced offspring general intelligence and executive function via offspring PGS (genetic pathway) and parental education (phenotypic pathway). Similar results were found for the parental PGS for educational attainment and offspring reading and writing skills. These pathways fully explained associations between parental PGS and offspring phenotypes, without residual direct association. Associations with maternal, but not paternal, PGS were replicated. No associations were found between parental PGS for psychopathology and offspring specific symptoms.

Conclusions: Our findings indicate that parental genetics influences offspring cognition and educational attainment by genetic and phenotypic pathways, suggesting targeting parental traits such as education can influence child development above and beyond genetic factors. Multiple mediations might represent an effective approach to study modifiable factors for phenotypic transmission.

Key words: genetics; gene-environment correlation; intergenerational transmission; cognition; educational attainment; polygenic scores.

INTRODUCTION

How parents influence offspring's behavior is an essential question for mental health sciences and remains unclear. Understanding specific pathways by which phenotypes are "transmitted" may clarify developmental cascades underlying the emergence of psychopathology and cognitive outcomes[1], which might help selecting preventive measures.

Each parent transmits half of their nuclear DNA to their offspring, influencing children's genetic susceptibility to traits. Common genetic liability can be indexed using polygenic scores (PGS), which predict around 11-13% of educational attainment variance and 7–10% of cognitive performance variance[2]. Parental genetics can also influence parental behaviors and, consequently, the environment in which their offspring live (passive gene-environment correlation), which can in turn impact children's phenotypes[3]. Parents with higher levels of education, for instance, can provide a family environment that facilitate success in their offspring educational attainment[4], including higher parental and neighborhood socioeconomic status[5] and higher number of books at home[6,7].

Few studies have tried to separate and quantify genetic and environmental influences on offspring education, cognition and psychopathology, using natural experiments[8], twin[9–12] and adoption studies[13,14]. More recently, molecular genetic studies have applied PGS to multiple statistical models, including (1) adjusting maternal PGS for offspring PGS[15,16], (2) creating PGS for transmitted and non-transmitted alleles ("genetic nurture") [4,17,18], and (3) creating similarity matrices between offspring and parental genotypes to investigate their covariance on offspring phenotypes[19,20].

Previous evidence is limited in important ways. Behavioral genetic studies are often constrained to very specific situations (e.g., *in vitro* fertilization and adoption), which might not be generalizable to other populations. Moreover, most molecular genetic studies do not account for the effects of parental traits and, consequently, cannot investigate direct and indirect influences that parental genes might have on offspring behavior via parental phenotypes. Therefore,

although these methods can estimate how much of transmission is explained by genetic vs gene-environment effects, they cannot indicate which specific factors are implicated in this process, which could help evaluating the potential impact of preventive strategies targeting parental phenotypes.

Here we aim to investigate pathways by which maternal and paternal PGS for cognition, educational attainment, ADHD, and schizophrenia influence related phenotypes among offspring in two samples of youth. We use a stepwise regression-based approach and multiple mediation models to analyze the effect of offspring PGS (genetic pathway) and parental phenotype (phenotypic pathway) on children's cognition, education and psychopathology in a Brazilian sample. Significant results will also be tested in a replication sample of French-Canadian adolescents. Given that parental genes can affect both parental phenotypes and offspring genetic susceptibility to traits, which could both in turn affect offspring phenotypes, we hypothesize that parental PGS for cognition, educational attainment, ADHD and schizophrenia will predict offspring cognition, educational outcomes and psychopathology via offspring PGS and their corresponding parental phenotypes. We selected these PGS given their higher predictive capacity of phenotypes.

METHODS

Main sample

1. Participants and sample

Participants were offspring and parents from the Brazilian High Risk Cohort Study for Mental Conditions (BHRCS[21]). Offspring were aged 6-14 years (at baseline), recruited from 57 schools in Porto Alegre and São Paulo, Brazil. In the screening phase, primary caregivers (87.3% mothers) from 8012 families with 9937 eligible children were interviewed about family psychiatric symptoms using a modified version of the Family History Screen (FHS[22]). Afterwards, a high-risk subgroup for psychiatric disorders composed of 1553 participants with psychiatric symptoms and

high family loading of symptoms, and a randomly selected sample of 958 individuals were selected (total sample= 2,511). From this sample, 2189 offsprings, 1898 mothers and 1017 fathers underwent genotyping and psychiatric assessment[21]. Offsprings also underwent cognitive evaluation. Phenotypic measures used in this study were collected at baseline (2009/2010).

2. *Ethical considerations*

Participants and parents provided written and/or verbal consent. This study was approved by the Ethics Committee of the University of São Paulo and of the Hospital de Clínicas de Porto Alegre.

3. Genotyping and polygenic scores

We isolated genomic DNA from saliva (Oragene) using prepIT-L2P reagent (DNAgenotek). Genotyping was performed using the Global Screening Array (Illumina). Single nucleotide variants (SNV) with minor allele frequency <1%, locus missingness >10%, or Hardy-Weinberg equilibrium significance <0.000001 were excluded, such as individuals with genotype missingness >10% and an estimation of identity by descent >0.12.

We calculated PGS for offspring, mothers and fathers using PRSice v2.3.3 software, based on summary statistics from previous genome-wide association studies (GWAS) for cognition and educational attainment[2], ADHD[23], and schizophrenia[24]. P-value-informed clumping was performed retaining the SNV with the smallest p-value within a 250-kb window and excluding SNVs in linkage disequilibrium (r2 >0.1). We also calculated 10 principal components for the trios to adjust for ancestry.

We selected the PGS p-threshold with highest variance explained for parental phenotypes (i.e., parental education for cognition and educational attainment PGS and specific ADHD and

schizophrenia symptoms for their corresponding PGS) using PRSice v2.3.3 (Supplemental material). For analyses using offspring PGS, we selected the same p-threshold as used for the main PGS in the analysis (e.g., the best p-threshold for the mother in analyses with maternal data).

4. Phenotypic measures

4.1. Offspring

4.1a. Cognition

General intelligence (IQ) was measured using the vocabulary and block design subtests of the Wechsler Intelligence Scale for Children, third edition (WISC-III)[25] applied by trained psychologists. Full-scale IQ was estimated using the Tellegen and Briggs formula, adjusted by age and standardized using Brazilian norms[26].

Global executive function was assessed combining tasks that evaluated working memory, inhibitory control, and time processing[21,27] (Supplemental material). We used generalized additive models to regress out the effects of age and sex on task performance. Global executive function was then calculated using a second order model encompassing all tasks, which presented excellent fit[27].

4.1b. Educational attainment

Reading and writing skills were quantified using the Brazilian version of the Academic Performance Test[28], in which participants read aloud 70 words and write 34 dictated items. Dependent variables for reading and writing skills were factor scores for each task after regressing out age trends by saving studentized residuals.

4.1c. Psychopathology

ADHD symptoms were assessed using the sum of items from the Development and Well-Being Assessment (DAWBA) Section for ADHD[29], while schizophrenia symptoms were assessed using the sum of items from the Community Assessment of Psychic Experiences (CAPE) positive symptoms subscale[30] (Supplemental material).

4.2. Parents

Educational attainment was assessed for both parents with a specific question for the primary informant regarding parental educational level, composed of eight levels varying from "none" to "higher education with postgraduate studies".

Parental specific psychopathology was assessed using the sum of specific items for ADHD and schizophrenia of the FHS. Previous studies showed acceptable tests–retest reliability and accuracy for most diagnoses[22].

Replication sample

The replication sample was composed of adolescents and their parents from the Saguenay Youth Study (SYS), a French-Canadian family-based cohort[31]. Inclusion criteria were: (1) age 12-18 years; (2) one or more siblings in the same age group; (3) all grandparents with French-Canadian ancestry and born in the region. Adolescents were recruited from high schools in the region. Data were collected for 1029 adolescents (from 481 families) and 962 parents using telephone interviews, home, laboratory and school visits. From this sample, neuropsychological and genotyping data were obtained from the full adolescent sample, 363 mothers and 307 fathers. Genome-wide genotyping was performed with the Human610-Quad and HumanOmniExpress BeadChips (Illumina, San Diego, CA) using DNA from peripheral blood cells. PGS for cognition and educational attainment were calculated as described for the main sample, using the PGS p-threshold with highest variance explained for parental phenotypes as well (see Supplemental material).

Parental education was assessed with a specific question for the primary informant (99% mothers) about parental educational level, composed of seven levels varying from “elementary school” to “University superior cycle”. Cognitive assessments for offsprings were performed by trained psychometricians. General intelligence was evaluated using the WISC-III[32]. Executive function was investigated using specific tests (self-ordered pointing, word fluency, resistance to interference). Reading and writing skills were assessed using the reading comprehension and a spelling test from the Woodcock–Johnson Achievement test. Further information can be found elsewhere[31,33].

Statistical analyses

We followed a stepwise approach in which analyses had to be statistically significant to continue to the next step. Analyses were performed separately for mothers and fathers. *First*, we tested separately whether parental PGS were associated with corresponding parental phenotype, offspring PGS and offspring phenotypes and whether offspring PGS and parental phenotypes were associated with offspring phenotypes. *Second*, we used multiple mediations with structural equation models[34] to test whether parental PGS and offspring phenotypes were associated directly and/or if this association was mediated by the corresponding offspring PGS (genetic pathway) and/or parental phenotype (phenotypic pathway). *Third,* for significant analyses in both steps, we performed the following supplemental analyses: (1) given that adjusting for the effect of one of the parents PGS on offspring PGS could lead to a potential collider bias (e.g., a positive association with maternal PGS could lead to a negative association with paternal PGS or *vice versa*[35]), we repeated these models adding the other parent PGS as a third mediator; (2) given that individuals often choose partners with similar phenotypes (i.e., assortative mating[36]), we also repeated the multiple mediations described in step 2 adding the other parent phenotype as a third mediator; (3) we investigated pleiotropic effects by repeating multiple mediations using outcomes

that were not corresponding to the PGS (e.g., PGS for cognition with reading and writing skills and the PGS for educational attainment with general intelligence and executive function).

In analyses using the PGS for cognition and educational attainment, we used the corresponding offspring PGS as a mediator in the genetic pathway and parental educational level as a mediator in the phenotypic pathway. As outcomes, we used offspring IQ and executive function in analyses with the PGS for cognition and reading and writing skills in analyses with the PGS for educational attainment. In analyses with the PGS for ADHD and schizophrenia, we used corresponding offspring PGS and parental corresponding symptoms as mediators and offspring specific symptoms as outcome.

In separate regressions, we adjusted parental PGS for ancestry using their 10 principal components (PC) as covariates. For multiple regressions, we regressed out the effect of 10 PC of parents and offspring on their respective PGS to simplify the analysis and facilitate the use of this approach in different mediation softwares. In these analyses, we used the full information maximum likelihood (FIML) method[37]. As a *post-hoc* analysis, we investigated whether age ($\leq$10 years of age, n=880, vs >10 years or older, n=1018) moderated genetic or environmental pathways by using multiple moderated meditations for significant analyses.

Analyses that yielded significant results in the discovery sample were repeated in the replication sample using the same step-wise approach and regression models. However, given that the replication sample included data from siblings, we added family identification as cluster in multiple mediations.

RESULTS

PGS for cognition and educational attainment

Separate regressions

Sample description can be found in Table 1. We found that both maternal and paternal PGS for cognition and for educational attainment were associated with offspring corresponding PGS (mediator 1), respective parent educational level (mediator 2) and offspring phenotypes (outcomes). We also found that both mediators were associated with offspring phenotypes (Table S1).

Analyses with maternal PGS were replicated in the SYS sample, except for the association between the maternal PGS for educational attainment and offspring writing skills (Supplemental material). However, no associations were found between paternal PGS and paternal education or between paternal PGS and any offspring phenotypes in the replication sample. Therefore, we did not perform further analyses with paternal PGS data for the replication sample

Multiple mediations

In the discovery sample, we found that associations between maternal and paternal PGS for cognition and offspring general intelligence and executive function were fully mediated by offspring PGS for cognition (genetic pathway) and parental educational level (phenotypic pathway), with no direct effect (Table 2 and 3). We found similar results for associations between both maternal and paternal PGS for educational attainment and offspring reading and writing skills (Figure 1). Similar results were found in the replication sample for the associations of the maternal PGS for cognition with offspring general intelligence and executive function, and between the maternal PGS for education and offspring reading skills (Supplemental material).

Multiple mediations adjusting for collider bias and assortative mating

The above results were similar when adjusting for collider bias (i.e., other parent corresponding PGS), except for absence of mediation of the genetic pathway on the association between maternal PGS for cognition and offspring IQ (Table S2).

Results were also similar for maternal PGS for cognition when adjusting for assortative mating (i.e., paternal educational level), with no evidence of mediation of the genetic pathway on the association with offspring IQ (Table S3). For the maternal PGS for educational attainment, however, we found that associations with offspring reading and writing skills were also mediated by paternal education, which might be evidence for assortative mating. In analyses with paternal PGS, we found no evidence of assortative mating, but associations via phenotypic pathway were no longer significant when adjusting for maternal education.

We did not find evidence of either collider bias nor assortative mating in the replication sample (Table S7 and S8).

Pleiotropy

We found that both maternal and paternal PGS for educational attainment were associated with offspring IQ and executive function and that both maternal and paternal PGS for cognition were associated with offspring reading and writing skills in the discovery sample (Table S5). These associations were fully mediated by genetic and phenotypic pathways.

Moderated multiple mediations

For the analyses with the maternal PGS for educational attainment, we found that age moderated the association between offspring PGS and reading and writing skills (see Table S6). This association was only significant for children younger than 10 years of age. We did not find evidence of moderation on the phenotypic pathway or for other PGS.

PGS for psychopathology

We found that maternal PGS for schizophrenia was associated with maternal corresponding symptoms and that maternal ADHD symptoms were associated with offspring corresponding symptoms (Table S4). No associations were found for paternal PGS for

psychopathology and either paternal or offspring symptoms or between offspring PGS and offspring symptoms. Therefore, we did not perform further analyses with psychopathology data.

DISCUSSION

We found that both maternal and paternal PGS for cognition were associated with offspring general intelligence and executive function through genetic (via offspring PGS) and phenotypic pathways (via parental educational level). Similar results were found for parental PGS for education and offspring reading and writing skills. These mediations seemed to fully explain the relationship between parental PGS and offspring phenotypes, without residual direct association between these variables. Findings with maternal PGS for cognition and offspring general intelligence and executive function and maternal PGS for educational attainment and offspring reading skills were replicated in a distinct sample from diverse cultural and ancestry backgrounds. Results were similar when adjusting for collider bias (other parent PGS). Moreover, we found that associations between maternal PGS for educational attainment and offspring reading and writing skills were also mediated by paternal education in the discovery sample, which might suggest assortative mating, but this result was not replicated. We also found evidence of pleiotropy for the PGS for cognition and educational attainment.

These findings are in agreement with previous studies, which estimated the genetic nurture effect for educational outcomes to be around half of the genetic effect (β=0.08 x β=0.17, respectively), with similar effect for mothers and fathers and with larger effect size when using parental PGS adjusted by offspring PGS compared with non-transmitted and transmitted PGS[38]. Our findings go beyond past knowledge by indicating that part of this genetic nurture effect might be represented by parental education, suggesting targeting parental education could improve offspring cognition and educational attainment. We also explored associations with the PGS for cognition, which, to our knowledge, had not been investigated before.

Surprisingly, associations between paternal PGS and offspring phenotypes were not replicated. This could be due to lower power given the smaller sample size (n=1017 for the discovery sample vs n=307 for the replication sample). It could also be due to genetic and/or cultural differences between these samples, given the distinct ethnicities (admixed Brazilian sample vs French-Canadian sample) and socioeconomic backgrounds (middle vs high-income country).

Furthermore, we did not find associations between parental PGS for ADHD and schizophrenia and offspring specific symptoms. This could be due to smaller variances explained for these PGS (5.5% for ADHD[23] and 8% for schizophrenia[24]) and/or to smaller influences of parental behavior on offspring specific symptoms. Previous studies found that offspring ADHD symptoms were only associated with parental transmitted PGS for ADHD, but not with non-transmitted PGS, suggesting that influences that parental genes have on environment do not affect offspring's susceptibility to ADHD[39].

To our knowledge, this is the first study to use multiple mediations to investigate associations between parental genotype and offspring phenotypes. Differently from other methods, this approach makes it possible not only to estimate how much of the influences parental genetics have on offspring phenotypes is due to genetic and/or environmental factors, but the specific mechanisms by which these associations occur. Therefore, they can help clarifying pathways of intergenerational transmission of educational disadvantage, cognition impairment and psychopathology and suggest which parental phenotypes could be targeted to break the cycle of transmission of these conditions. This method can also be used in more complex models to understand how this transmission is affected by other demographic and environmental/phenotypic factors, such as parental cognition, social skills or time spent with offspring.

This study has limitations to be addressed. First, these PGS were based on GWAS for European samples, and therefore effect sizes might be attenuated by the lower precision of PGS

scores in admixed samples. Nonetheless, analyses with maternal PGS were replicated in a European ancestry sample. Second, adjusting for the effect of parental PGS on offspring PGS could lead to a collider bias. However, results remained similar when using paternal PGS as a third mediator. Third, using multiple PGS and phenotypes could increase type 1 error. Nevertheless, using a stepwise approach, which reduces the number of models being tested, and a replication sample decrease this possibility.

CONCLUSION

We found that parental genetics impacts offspring cognitive and educational phenotypes by influencing both offspring genetics and parental phenotypes, suggesting that targeting parental education can influence youth general intelligence, executive function and language skills above and beyond genetic factors. Our findings suggest multiple mediations are an innovative approach to study specific genetic and phenotypic pathways for intergenerational transmission of traits. Future studies can use this approach to investigate different PGS and phenotypes, as well as create more complex models to analyze how this transmission is influenced by other genetic and environmental factors.

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KEY POINTS

- Most previous studies cannot indicate specific factors implicated in the intergenerational transmission of cognition, education and psychopathology.
- Using multiple mediation models, we found maternal and paternal polygenic scores (PGS) for cognition influenced offspring general intelligence and executive function via offspring PGS (genetic pathway) and parental education (phenotypic pathway), without residual direct association. Similar results were found for the parental PGS for educational attainment and offspring reading and writing skills.
- Associations with maternal data, but not paternal, replicated in an independent sample.
- Parental education might be a target to improve offspring general intelligence, executive function, reading and writing skills.
- Multiple mediations seem an effective approach to identify specific pathways for phenotypic transmission.

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Figure 1. Results of main analyses for maternal polygenic score (PGS) for educational attainment and offspring reading

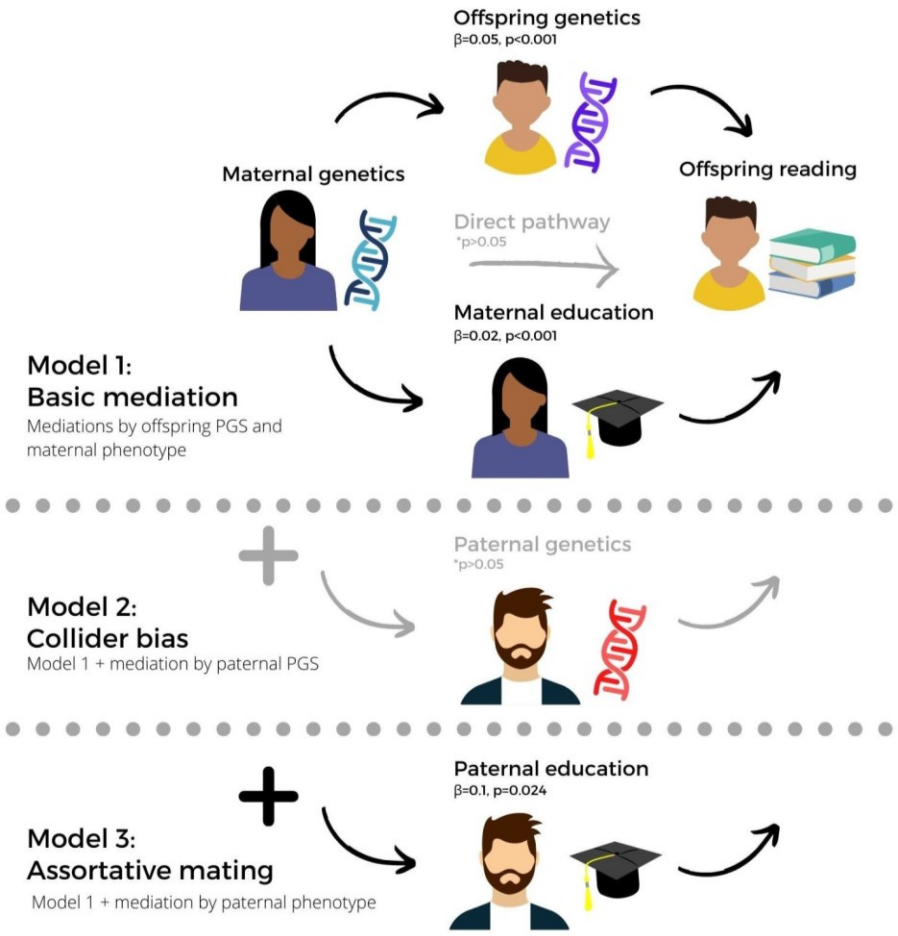

Table 1. Samples description.

1a. Offspring

	Discovery sample (n=2189)	Replication sample (n=1089)
Mean age (SD)	10.2 (1.92)	15.0 (1.84)
Male sex	1195 (54.6%)	494 (48%)
Ethnicity		
White	1316 (60.1%)	1029 (100%)
Black	228 (10.4%)	-
Multiracial	628 (28.7%)	-
Others	17 (0.8%)	-

1b. Parents

	Discovery sample		Replication sample	
	Mothers (n=1898)	Fathers (n=1017)	Mothers (n=363)	Fathers (n=307)
Mean age (SD)	36.3 (6.9)	40.5 (8.17)	47.9 (4.7)	51.1 (4.7)
Educational level (complete or incomplete)				

Illiterate/ no education	38 (2%)	26 (2.6%)	0 (0%)	0 (0%)
Elementary school	721 (38%)	457 (44.9%)	16 (4.3%)	12 (3.9%)
High school	978 (51.5%)	459 (45.1%)	118 (32.5%)	118 (38.4%)
Higher education	161 (8.5%)	75 (7.4%)	229 (63.2%)	177 (57.7%)

Table 2. Results for multiple mediations analyses using maternal PGS for cognition and educational attainment as predictors (X), offspring corresponding PGS as mediator 1 (M1), maternal educational as mediator 2 (M2) and offspring cognitive phenotypes as outcomes (Y) for discovery and replication samples.

	Direct effect *(X = maternal PGS)*		Genetic pathway *(M1 = offspring PGS)*		Phenotypic pathway *(M2 = maternal education)*		Total effect	
	β	p	β	p	β	p	β	p
Discovery sample								
PGS for cognition								
IQ	0.027	0.307	**0.026**	**0.044**	**0.015**	**0.006**	**0.068**	**0.004**
Executive function	0.010	0.707	**0.053**	**<0.001**	**0.011**	**0.008**	**0.074**	**0.001**
PGS for educational attainment								
Reading	-0.004	0.892	**0.050**	**<0.001**	**0.018**	**<0.001**	**0.064**	**0.009**
Writing	-0.008	0.767	**0.053**	**<0.001**	**0.016**	**<0.001**	**0.061**	**0.012**
Replication sample								
PGS for cognition								
IQ	0.154	0.774	**0.047**	**0.002**	**0.033**	**0.019**	**0.093**	**0.035**

Executive function	0.055	0.191	**0.048**	**0.006**	**0.086**	**0.029**	**0.126**	**0.002**
PGS for educational attainment								
Reading	0.053	0.150	**0.031**	**0.024**	**0.027**	**0.014**	**0.110**	**0.004**

Note: bold analyses are significant at the $p<0.05$ level.

Table 3. Results for multiple mediations analyses using the paternal PGS for cognition and educational attainment for the discovery sample.

	Direct effect *(X = paternal PGS)*		Genetic pathway *(M1 = offspring PGS)*		Phenotypic pathway *(M2 = paternal education)*		Total effect	
	β	p	β	p	β	p	β	p
PGS for cognition								
IQ	0.059	0.131	**0.062**	**0.001**	**0.018**	**0.019**	**0.139**	**<0.001**
Executive function	0.021	0.428	**0.056**	**<0.001**	**0.008**	**0.037**	**0.084**	**<0.001**
PGS for educational attainment								
Reading	0.022	0.595	**0.051**	**0.010**	**0.020**	**0.006**	**0.093**	**0.014**
Writing	0.011	0.801	**0.052**	**0.009**	**0.018**	**0.009**	**0.081**	**0.034**

Note: bold analyses are significant at the p<0.05 level.