A Polygenic Score for Higher Educational Attainment is Associated with Larger Brains

Maxwell L. Elliott1*
Daniel W Belsky2-3*
Kevin Anderson4
David L. Corcoran5
Tian Ge6-8
Annchen Knodt1
Joseph A. Prinz5
Karen Sugden3,5
Benjamin Williams3,5
David Ireland9
Richie Poulton9
Avshalom Caspi1,5,10-11
Avram Holmes4
Terrie Moffitt1,5,10-11
Ahmad R Hariri1

1. Department of Psychology & Neuroscience, Duke University Box 104410, Durham, NC 27708, USA
2. Department of Population Health Sciences, Duke University School of Medicine, Box 3003, Durham, NC 27710, USA
3. Social Science Research Institute, Duke University, Box 90989, Durham, NC 27708, USA
4. Department of Psychology, Yale University, New Haven, CT 06511, USA
5. Center for Genomic and Computational Biology, Duke University Box 90338, Durham, NC 27708, USA
6. Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA 02129, USA
7. Psychiatric and Neurodevelopmental Genetics Unit, Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA 02114, USA
8. Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, Cambridge, MA, USA
9. Dunedin Multidisciplinary Health and Development Research Unit, Department of Psychology, University of Otago, 163 Union St E, Dunedin, 9016, NZ
10. Social, Genetic, & Developmental Psychiatry Research Centre, Institute of Psychiatry, Psychology, & Neuroscience, King’s College London, De Crespigny Park, Denmark Hill, London SE5 8AF, UK
11. Department of Psychiatry & Behavioral Sciences, Duke University School of Medicine, Durham, NC 27708, USA

Abstract word count: 185
Manuscript word count: 3262
Number of tables: 1
Number of figures: 4

*These authors contributed equally to this work and are the lead authors
Acknowledgement. This research was conducted using the UK Biobank Resource (project ID #28174). The Dunedin Multidisciplinary Health and Development Study is supported by the NZ HRC, NZ MBIE, National Institute on Aging grant R01AG032282, R01AG049789, and UK Medical Research Council grant MR/P005918/1. The Duke Neurogenetics Study received support from Duke University as well as US-National Institutes of Health grants R01DA033369 and R01DA031579. MLE is supported by the National Science Foundation Graduate Research Fellowship under Grant No. NSF DGE-1644868. DWB is supported by an early-career fellowship from the Jacobs Foundation. TG is supported by National Institutes of Health grant K99AG054573. AJH is supported by National Institute of Mental Health grant K01MH099232. Thank you to members of the Advisory Board for the Dunedin Neuroimaging Study. The authors declare no competing financial interests.
Abstract. People who score higher on intelligence tests tend to have larger brains. Twin studies suggest the same genetic factors influence both brain size and intelligence. This has led to the hypothesis that genetics influence intelligence partly by contributing to development of larger brains. We tested this hypothesis using 4 large imaging genetics studies (combined N=7,965) with polygenic scores derived from a genome-wide association study (GWAS) of educational attainment, a correlate of intelligence. We conducted meta-analysis to test associations among participants’ genetics, total brain volume (i.e., brain size), and cognitive test performance. Consistent with previous findings, participants with higher polygenic scores achieved higher scores on cognitive tests, as did participants with larger brains. Participants with higher polygenic scores also had larger brains. We found some evidence that brain size partly mediated associations between participants’ education polygenic scores and their cognitive test performance. Effect-sizes were larger in the population-based samples than in the convenience-based samples. Recruitment and retention of population-representative samples should be a priority for neuroscience research. Findings suggest promise for studies integrating GWAS discoveries with brain imaging to understand neurobiology linking genetics with cognitive performance.
Introduction

People who score higher on tests of intelligence tend to have larger brains, as measured by ex-vivo brain weight and in-vivo magnetic resonance imaging (MRI) (van Valen 1974; Haier et al. 2004; McDaniel 2005; Pietschnig et al. 2015). Twin studies indicate this relationship partly reflects genetic factors that influence both brain size (i.e., volume) and intelligence (Posthuma et al. 2003; Toga and Thompson 2005; Deary et al. 2010; Posthuma et al. 2002). These findings suggest the hypothesis that one path through which genetic differences between people influence individual differences in intelligence is by contributing to the development of larger brains. This hypothesis can now be tested using molecular genetic data.

A recent genome-wide association study (GWAS) of educational attainment identified dozens of genetic variants that showed substantial enrichment for genes expressed during brain development (Okbay et al. 2016). Follow-up studies further identified associations between an aggregate measure of GWAS-discovered influences on education, called a polygenic score, and intelligence, including in young children who had not yet entered school (Belsky et al. 2016; Selzam et al. 2017). These findings implicate brain development and intelligence in the pathway connecting people’s genetics to their educational outcomes. Further, GWAS research has discovered polygenic variants associated with brain size (inferred through intracranial volume) (Adams et al. 2016) that also overlap with variants associated educational attainment (Okbay et al. 2016). Now, studies are needed to test if genetics discovered in GWAS of education are associated with in-vivo intermediate phenotypes, like brain size, that could constitute a biological pathway linking genetic variation to differences in intelligence and educational attainment.

We analyzed data from four imaging genetics studies from the United Kingdom (UK Biobank), New Zealand (Dunedin Study), and the United States (Brain Genomics Superstruct...
Project (GSP) and Duke Neurogenetics Study (DNS)), including 7,965 participants, to test
associations among a polygenic score for educational attainment, cognitive test performance, and
brain size. We hypothesized that, consistent with previous findings, (1) participants with higher
education polygenic scores would have higher cognitive test scores; and (2) that participants with
larger brains as measured by total brain volume would have higher cognitive test scores. We
further posed the novel hypotheses that (3) participants with higher education polygenic scores
would have larger brains and that brain size would mediate the association between the education
polygenic score and cognitive test performance. We combined results across our four imaging
genetics datasets using random-effects meta-analysis. We also examined heterogeneity between
the datasets under the hypothesis that effect-sizes might differ between the population-based UK
Biobank and Dunedin Study samples and the GSP and DNS samples, for which range in
cognitive performance is more restricted.

Methods

Participants. We analyzed data from European-descent participants in the United Kingdom-
based UK Biobank (Sudlow et al. 2015; Miller et al. 2016) a population-based volunteer sample
(N=5691), the New Zealand-based Dunedin Study, a population-representative birth cohort
(N=596) (Poulton et al. 2015), and two studies in the United States consisting primarily of
university students, the Brain Genomics Superstruct Project(Holmes et al. 2015) (GSP, N=1163),
and the Duke Neurogenetics Study (Elliott et al. 2018) (DNS, N=515). Sample sizes reflect
participants with available structural MRI, cognitive testing, and genetic data (Table 1). Samples
are described in detail in the supplement and Table 1.
**Education Polygenic Score.** We computed our polygenic score based on GWAS of educational attainment rather than GWAS of cognitive performance because educational attainment is a proxy phenotype for cognitive performance (Rietveld et al. 2014) and the polygenic score for educational attainment is more predictive of cognitive performance than polygenic scores from GWAS of cognitive performance (Plomin and von Stumm 2018). Education polygenic scores were computed from genome-wide single-nucleotide polymorphism (SNP) data based on GWAS results published by the Social Science Genetics Association Consortium (Okbay et al. 2016) following methods described by Dudbridge (Dudbridge 2013) according to the procedure used in our previous work (Belsky et al. 2016). Genetic data from the Dunedin study were imputed to 1000 Genomes (Abecasis et al. 2012), data from all other studies were not imputed. Following established practice (Wray et al. 2007; Dudbridge 2013; Okbay et al. 2016), we computed polygenic scores using data from all SNPs included in the EA2 GWAS. SNPs were not clumped or pruned for LD prior to analysis (Ware et al. 2017). Briefly, for each study, we matched SNPs in the study’s genetic database with published educational attainment GWAS results (Okbay et al. 2016). We then multiplied the education-associated allele of each SNP by the GWAS-estimated effect-size and computed the average of these products across all SNPs. Polygenic scores were standardized within each study to have M=0, SD=1 for analysis.

**Cognitive Performance.** Cognitive performance was measured in the UK Biobank using 13 reason and logic puzzles (Lyall et al. 2016). Cognitive performance was measured in the Dunedin Study, GSP, and DNS studies using intelligence tests (the Wechsler Adult Intelligence Scale (WAIS-IV) (Wechsler 1997) in the Dunedin Study, the Shipley Institute of Living Scale
(Zachary 1986) in GSP and the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler 2013) in the DNS).

**Total Brain Volume.** Total brain volume was measured from high resolution, T1-weighted MRI images. In the UK Biobank total brain volume was estimated using SIENAX (Smith et al. 2002). In the Dunedin Study, GSP, and DNS studies, images were processed using the Freesurfer processing pipeline.

**Statistical Analyses.** We tested associations using linear regression models. Models were adjusted for sex. Models including the polygenic score were adjusted for the first 10 principal components estimated from the genome-wide SNP data to account for any residual population stratification within the European-descent samples analyzed (Price et al. 2006). Models of UK biobank and GSP data were adjusted for age. (The Dunedin Study is a single-year birth cohort and DNS participants vary in age by only by 1-2 years.). In addition to age, models in the GSP were also adjusted for scanner, console version and head coil (12 versus 32 channel) because the GSP was collected across multiple sites. Analyses of individual studies were conducted in R (version 3.4.0). Linear regressions were performed using the lm function. Mediation analyses were performed using a system of equations approach (Preacher and Hayes 2008) implemented with the mediation package(Tingley et al. 2014) in R, using nonparametric bootstrapping with 1000 iterations. The system of equations includes 3 regressions. The first regression tests association between the predictor (PGS) and outcome (IQ). The second regression tests association between the predictor (PGS) and the mediator (TBV). The third regression tests multivariate association between the predictor (PGS) and outcome (IQ) with covariate
adjustment for the mediator (TBV). If the regression coefficient between predictor and outcome is significantly smaller in the third model than the first, the inference of mediation is made. Coefficients from these regressions are combined using the formula originally proposed by Sobel (Sobel 2007). Standard errors are computed using the bootstrap method described in Preacher & Hayes (Preacher and Hayes 2008). We combined estimates across studies using random effects meta-analysis (DerSimonian and Laird 1986) implemented using STATA (version 15).

**Results**

**Participants with higher polygenic scores performed better on cognitive tests.** As anticipated, participants with higher polygenic scores performed better on cognitive tests. Meta-analysis estimated the cross-study effect size as $r=.18$ ($p<.001$; 95% CI [.11, .24]) with evidence of heterogeneity in effect sizes across studies (I-squared 83%, $p=.001$; tau-squared=.004). Effect sizes were statistically significant in UK Biobank ($r=.17$, $p<.001$), Dunedin Study ($r=.28$, $p<.001$) and GSP ($r=.19$, $p<.001$) but not in the DNS ($r=.05$, $p=.22$).

**Participants with larger brains had higher cognitive test scores.** We next tested if participants with larger brains performed better on cognitive tests. As anticipated, participants with larger brains (i.e., those with higher total brain volume) performed better on cognitive tests. Meta-analysis estimated the cross-study effect size as $r=.20$ ($p<.001$; 95% CI [.12, .29]) with evidence of heterogeneity in effect sizes across studies (I-squared=75.8%, $p=.002$; tau-squared=.005). Effect-sizes were statistically significant in all studies (UK Biobank $r=.19$, $p<.001$; Dunedin Study $r=.35$, $p<.001$; GSP $r=.12$, $p=.002$; DNS $r=.16$, $p=.004$).
Participants with higher polygenic scores for educational attainment had larger brains in two samples. Finally, we tested if participants with higher polygenic scores tended to have larger brains. Meta-analysis estimated the cross-study effect-size as $r=0.06$ ($p=0.006; 95\%\; CI\; [.02,\; .10]$). The test for evidence of heterogeneity in effect sizes across studies was statistically significant at the alpha=0.05 level ($I^2=71.8\%,\; p=0.014;\; \tau^2=0.001$). Participants with higher polygenic scores had larger brains in the UK Biobank ($r=0.09,\; p<0.001$) and the Dunedin Study ($r=0.07,\; p=0.024$). Effect-sizes were smaller and not statistically significant in the GSP ($r=0.02,\; p=0.380$) and DNS ($r=0.04,\; p=0.288$).

Brain size was a weak mediator of the polygenic-score associations with cognitive test scores in two study samples. To test the hypothesis that larger brains mediated the polygenic score association with intelligence, we used the system of equations described by Baron and Kenny (Baron and Kenny 1986) and the methods described by Preacher et al. (Preacher and Hayes 2008). Meta-analysis estimated the cross-study indirect effect to be $b=0.01,\; 95\%\; CI\; [.00,\; .02],\; p=0.045$, with evidence of heterogeneity in effect sizes across studies ($I^2=79.5\%,\; p=0.003;\; \tau^2=0.000$). The mediation effect was statistically significant in the UK Biobank ($b=0.02,\; 95\%\; CI\; [.01,\; .02],\; p < 0.001$) and the Dunedin Study ($b=0.02,\; 95\%\; CI\; [.00,\; .05],\; p=0.028$). We did not find evidence of a mediation effect in the GSP ($b=0.00,\; 95\%\; CI\; [.00,\; .00],\; p=0.36$) or DNS ($b=0.01,\; 95\%\; CI\; [-.00,\; .02],\; p=0.24$) (for details see table S2).

Sensitivity analysis: Associations among polygenic scores, brain size, and cognitive test scores were partially attenuated by range restriction. UK Biobank and Dunedin Study participants’ polygenic scores, brain size, and cognitive test performance were positively
correlated, with similar effect-sizes (Dunedin-study effect-sizes for analyses including IQ were somewhat larger, possibly reflecting greater measurement precision of the WAIS as compared to the UK Biobank reason-and-logic-puzzle test). By comparison, effect-sizes for these associations were smaller among GSP and DNS participants. To test if this difference could reflect the relatively restricted range of cognitive test performance in the GSP and DNS samples relative to the population-based UK Biobank and Dunedin samples, we conducted sensitivity analysis. Cognitive test scores were on average, 1-1.5 SDs higher in the GSP and DNS samples as compared to the general population and 30-50% less variable, indicating restricted range (Table 1). Sensitivity analysis restricted the UK Biobank sample – the largest study in our analysis – to participants with cognitive test scores 1 SD above the mean (i.e. scores of 9-13; n=1,391) for which the variance was approximately 45% of the full-sample variance. In this restricted sample, associations among participants’ polygenic scores, brain size, and cognitive test performance were attenuated by roughly 1/3 to 1/2 relative to the full-sample estimates (Supplemental Table S3). Parallel analysis testing restriction at the other end of the cognitive test score distribution yielded similar results (Supplemental Table S4). Statistical correction of effect-sizes for range restriction using Thorndike’s formula (Stauffer and Mendoza 2001) yielded similar results (Supplemental Table S7).

**Discussion**

We analyzed data from four imaging-genetics studies in the UK, NZ, and US to test if genetic associations with cognitive performance were mediated by differences in brain size. As anticipated, we found that participants with higher educational-attainment polygenic scores tended to score higher on tests of cognitive performance, as did those with larger brains. We also
found new information, that participants with higher education polygenic scores tended to have larger brains. In mediation analysis, brain size accounted for only a small fraction of the association between participants’ educational attainment polygenic scores and their cognitive performance, and this mediation effect was statistically significant in the population-based UK Biobank and Dunedin samples, but not in the GSP and DNS samples.

Effect-size variation across the samples we analyzed followed a consistent pattern; effect-sizes were larger in the population-based UK Biobank and Dunedin Study samples than in the GSP and DNS samples (see figures and table S1). One reason for these differences may be the more restricted range of variation in cognitive performance in the GSP and DNS samples arising from, e.g. overrepresentation of university-educated individuals. Such range restriction biases association estimates (Mendoza and Mumford 1987; Bland and Altman 2011) and has previously been shown to bias brain imaging research (Falk et al. 2013; Lewinn et al. 2017). In these relatively high-IQ and restricted-range samples, average cognitive performance was 1-1.5 standard deviations above the general-population mean and the variance was reduced by 30-50%. We conducted sensitivity analysis in a UK Biobank subsample selected to have high cognitive performance similar to the GSP and DNS samples. In this sample with restricted range of cognitive test performance, effect-sizes were attenuated by roughly 30-50%. We obtained similar estimates when we performed a statistical correction for range restriction using Thorndike’s formula (Stauffer and Mendoza 2001). Selective observation of high-cognitive-performance individuals in the GSP and DNS samples may have contributed to the lower effect-size estimates in these samples and to overall heterogeneity across samples in our meta-analysis.

We acknowledge limitations of our current analyses, which can be addressed in future research. First, analyses were restricted to European-descent participants. We focused on
European-descent participants to match the population studied in the GWAS of educational attainment. Application of GWAS results from European-descent samples to compute polygenic scores for samples of different ancestry has uncertain validity (Martin et al. 2017). As GWAS of education and related phenotypes in non-European samples become available, replication in additional populations will be needed. Second, polygenic scores were measured with substantial error. Genetic effect-sizes thus represent lower-bound estimates. As larger-sample GWAS become available, error in polygenic score measurement will decline and effect-sizes can be expected to increase (Cesarini and Visscher 2017). A third education polygenic score is available, but we were unable to use EA3 to compare across cohorts because the discovery sample included all of UK Biobank (supplemental table S6 reports EA3 for the other samples).

Measurement error may also affect the other variables in our analysis. For example, as noted by Gignac & Bates (Gignac and Bates 2017), effect-size estimates from more-reliable cognitive tests, such as the Wechsler Adult Intelligence Scale administered in the Dunedin Study, tend to be larger compared to effect-size estimates from briefer less-reliable cognitive tests. We report effect-sizes disattenuated for estimated measurement error and reliability using the approach proposed by Tucker-Drob (Tucker-drob 2017) in Supplemental Table S8. Third, total brain volume is only one route through which the genetics linked with educational attainment could affect cognitive performance. We studied this specific phenotype because it is the best-replicated neural correlate of cognitive function (Pietschnig et al. 2015). As more refined neural phenotypes of cognitive function are developed, including measures of cortical thickness, surface area, gyrification, and brain function, it will be important to test their potential mediating role in linking genetics with cognitive performance. Importantly, the hunt for neural phenotypes mediating genetic associations with cognitive performance need not assume that education-
linked genetics directly affect brain development. For example, there is evidence that exposure to education increases cognitive performance (Ritchie and Tucker-Drob 2018). It could be that higher education-linked genetics, and higher IQs, lead to more education, which in turn enhances brain size and other neural phenotypes.

We also cannot rule out age differences as a potential explanation for the difference in findings between the population-based UK Biobank and Dunedin Study samples as compared to the GSP and DNS samples. UK Biobank and Dunedin Study participants were measured in midlife, whereas GSP and DNS samples primarily included young adults. Among midlife UK Biobank participants, restricting the range of cognitive performance to be similar to the GSP and DNS samples reduced effect-sizes for associations among polygenic scores, brain size, and cognitive test performance. Population-based samples including both young and midlife individuals with DNA, MRI, and cognitive testing are needed to evaluate whether genetic associations with brain volume and cognitive performance vary with age. A final concern is potential reverse causation between brain size and cognitive function. Higher cognitive ability and related educational and socioeconomic attainments may be protective of age-related decline in brain volume or they may promote brain development. As GWAS of these phenotypes become available, new and developing methods may help address this question (Burgess et al. 2015; Grotzinger et al. 2018). Ultimately, longitudinal studies with repeated measures of brain volume and cognition will be needed to further inform our understanding of the relationship between cognitive development and brain development.

Within the bounds of these limitations, our findings contribute to evidence that genetics discovered in GWAS of educational attainment influence brain development and cognitive function. Bioinformatic analysis of education GWAS results have identified enrichment of
variants near genes expressed in brain development, specifically neural proliferation, neural
development, and dendrite formation (Okbay et al. 2016). Epidemiologic analysis of an
education-GWAS-based polygenic score found that children who carried more education-
associated genetic variants scored higher on cognitive tests as early as age 5 and that polygenic-
score-associated differences in cognitive test scores grew larger from middle childhood through
adolescence (Belsky et al. 2016, 2018). Several studies have reported that an education-GWAS-
based polygenic score is predictive of cognitive test performance in adolescents and adults
(Domingue et al. 2015; Selzam et al. 2017; Plomin and von Stumm 2018). Here, we show that
adults with higher education-GWAS-based polygenic scores have larger brains and score higher
on cognitive tests as compared to peers with lower polygenic scores. Evidence for larger brains
as a statistical mediator of polygenic score associations with cognitive performance was mixed in
our analysis. But findings suggest promise for future neuroscientific investigation of education-
linked genetics. One design to complement formal mediation analysis is gene-environment
interaction analysis to test if exposures that slow brain growth or restrict brain size, e.g., Zika
virus (Calvet et al. 2016), diminish associations between genetics and cognitive performance.

Our finding that genetics associated with educational and socioeconomic attainments are
also related to brain volume has implications for research on effects of poverty on the developing
brain. Childhood poverty exposure is associated with smaller brain volumes (Luby et al. 2013;
Hair et al. 2015). Education polygenic scores also tend to be lower in children growing up in
poorer families, a gene-environment correlation that presumably reflects effects of education-
linked genetics on parents’ economic attainments, which children inherit along with their
genotypes (Belsky et al. 2016). Studies that include controls for education genetics could
complement intervention studies (Brody et al. 2017) to help rule out potential confounding in associations between poverty and brain development.

A challenge facing research on how genetics affect the brain is the lack of population-representative samples with available brain imaging data. Human brain-imaging research has typically been conducted in samples similar to those in the GSP and DNS whose data we analyzed (Sears 1986; Peterson and Merunka 2014). Our findings illustrate how studies of samples pre-selected for high levels of cognitive functioning and related characteristics impose limitations on analysis of cognition-related neurobiology. Opportunities to understand the brain afforded by 21st Century measurement technologies must still reckon with 20th Century discoveries about selection bias (Berkson 1946; Heckman 1979). Efforts to recruit more representative samples that reflect the full range of cognitive functioning in the population are needed.

Individual differences in cognitive performance have a partial genetic etiology (Plomin and Deary 2015; Plomin and von Stumm 2018). This genetic etiology should be evident in individual differences in brain biology. As GWAS discoveries for intelligence and related traits clarify genetic etiology, follow-up in genetically-informed brain imaging studies can shed light on the neurobiological correlates of this genetic variation. Our findings encourage enthusiasm for this research, but also highlight limitations of existing data resources. Recruiting and retaining samples that are representative of the general population must be a priority in neuroscience research.
References

Abecasis GR, Auton A, Brooks LD, DePristo MA, Durbin RM, Handsaker RE, Kang HM, Marth GT, McVean GA. 2012. An integrated map of genetic variation from 1,092 human genomes. Nature. 491:56–65.

Adams HHH, Hibar DP, Chouraki V, Stein JL, Nyquist PA, Rentería ME, Trompet S, Arias-Vasquez A, Seshadri S, Desrivières S, Beecham AH, Jahanshad N, Wittfeld K, Van Der Lee SJ, Abramovic L, Alhusaini S, Amin N, Andersson M, Arfanakis K, Aribisala BS, Armstrong NJ, Athanasiu T, Axelsson T, Beiser A, Bernard M, Bis JC, Blanken LME, Blanton SH, Bohlken MM, Boks MP, Bralten J, Brickman AM, Carmichael O, Chakravarty MM, Chauhan G, Chen Q, Ching CRK, Cuellar-Partida G, Braber A Den, Doan NT, Ehrlisch S, Filippi I, Ge T, Giddaluru S, Goldman AL, Gottesman RF, Greven CU, Grimm O, Griswold ME, Guadalupe T, Hass J, Haukvik UK, Halil S, Hofer E, Hoehn D, Holmes AJ, Hoogman M, Janowitz D, Jia T, Kaspervicute D, Kim S, Klein M, Kraemer B, Lee PH, Liao J, Liewald DCM, Lopez LM, Luciano M, Macare C, Marquand A, Matarin M, Mather KA, Matteisen M, Mazoyer B, McKay DR, McWhirter R, Milaneschi Y, Mirza-Schreiber N, Muetzel RL, Maniega SM, Nho K, Nugent AC, Loohuis LMO, Oosterlaan J, Papmeyer M, Pappa I, Pirpamer L, Pudas S, Pütz B, Rajan KB, Ramasamy A, Richards JS, Risacher SL., Roiz-Santíañez R, Rommelse N, Rose EJ, Royle NA, Rundek T, Sämann PG, Satizabal CL, Schmaal L, Schork AJ, Shen L, Shin J, Shumskaya E, Smith A V., Sprooten E, Strike LT, Teumer A, Thomson R, Tordesillas-Güetierrez D, Toro R, Trabzuni D, Vaidya D, Van Der Grond J, Van Der Meer D, Van Donkelaar MMJ, Van Eijk KR, Van Erp TGM, Van Roon J, Walton E, Westlye LT, Whelan CD, Windham BG, Winkler AM, Woldehawariat G, Wolf C, Wolters T, Xu B, Yanek LR, Yang J, Zijenbos A, Zwiers MP, Agartz I, Aggarwal NT, Almasy L, Ames D, Amouyel P, Andreassen OA, Arepalli S, Assareh AA, Barral S, Bastin ME, Becker DM, Becker JT, Bennett DA, Blangero J, Van Bokhoven H, Boomsma DI, Brodaty H, Brouwer RM, Brunner HG, Buckner RL, Buitelaar JK, Bulayeva KA, Cahn W, Calhoun VD, Cannon DM, Cavalleri GL, Chen C, Cheng CY, Cichon S, Cookson MR, Corvin A, Crespo-Facorro B, Curran JE, Czisch M, Dale AM, Davies GE, De Deus EJC, De Jager PL, De Zubicaray GI, Delanty N, Depondt C, Destefano AL, Dillman A, Djurovic S, Donohoe G, Drevet WC, Duggirala R, Dyer TD, Eks S, Espeseth T, Evans DA, Fedko IO, Fernández G, Ferrucci L, Fisher SE, Fleischman DA, Ford I, Foroud TM, Fox PT, Franck C, Fukunaga M, Gibbs JR, Glahn DC, Gollub RL, Göring HHH, Grabe HJ, Green RS, Gruber O, Gudnason V, Guelfi S, Hansell NK, Hardy J, Hartman CA, Hashimoto R, Hegenscheid K, Heinz A, Le Hellard S, Hernandez DG, Heslenfeld DJ, Ho BC, Hoekstra PJ, Hoffmann W, Hofman A, Holsboer F, Homuth G, Hosten H, Hottenga JJ, Pol HEH, Ikeda M, Ikram MK, Jack CR, Jenkinson M, Johnson R, Jönsson EG, Jukema JW, Kahn RS, Kanai R, Kloszewska I, Knoepfle MM, Kochunov P, Kwock JB, Lawrie SM, Lemaître H, Liu X, Longo DL, Longstreth WT, Lopez OL, Lovestone S, Martinez O, Martinot JL, Mattay VS, McDonald C, McIntosh AM, McMahon KL, McMahon FJ, Mecocci P, Melle I, Meyer-Lindenberg A, Mohrke S, Montgomery GW, Morris DW, Mosley TH, Mühlleisen TW, Müller-Myhsok B, Nalls MA, Nauck M, Nichols TE, Niessen WJ, Nöthen MM, Nyberg L, Ohi K, Olvera RL, Ophoff RA, Pandolfo M, Paus T, Pausova Z, Penninx BWJH, Pike GB, Potkin SG, Psaty BM, Reppermund S, Rietschel M, Roffman JL, Romanczuk-Seiferth N, Rotter JI, Ryten M, Sacco RL, Sachdev PS, Saykin AJ, Schmidt R, Schofield PR, Sigurdsson S, Simmons A, Singleton A, Sisodiya SM, Smith
C, Smoller JW, Soininen H, Srikanth V, Steen VM, Stott DJ, Sussmann JE, Thalamuthu A, Tiemeier H, Toga AW, Traynor BJ, Troncoso J, Turner JA, Tzourio C, Uitterlinden AG, Hernández MCV, Van Der Brug M, Van Der Lugt A, Van Der Wee NJA, Van Duijn CM, Van Haren NEM, Van’t Ent D, Van Tol MJ, Vardarajan BN, Veltman DJ, Vernooij MW, Völzke H, Walter H, Wardlaw JM, Wassink TH, Weale ME, Weinberger DR, Weiner MW, Wen W, Westman E, White T, Wong TY, Wright CB, Zielke HR, Zonderman AB, Deary IJ, Decarli C, Schmidt H, Martin NG, De Craen AJM, Wright MJ, Launer LJ, Schumann G, Fornage M, Franke B, Debette S, Medland SE, Ikram MA, Thompson PM. 2016. Novel genetic loci underlying human intracranial volume identified through genome-wide association. Nat Neurosci. 19:1569–1582.

Baron RM, Kenny DA. 1986. The Moderator Mediator Variable Distinction in Social Psychological Research - Conceptual, Strategic, and Statistical Considerations. J Pers Soc Psychol. 51:1173–1182.

Belsky DW, Domingue BW, Wedow R, Arseneault L, Boardman JD, Caspi A, Conley D, Fletcher JM, Freese J, Herd P, Moffitt TE, Poulton R, Sicinski K, Wertz J, Harris KM. 2018. Genetic analysis of social mobility in five longitudinal studies. Proc Natl Acad Sci. In Press.

Belsky DW, Moffitt TE, Corcoran DL, Domingue B, Harrington H, Hogan S, Houts R, Ramrakha S, Sugden K, Williams BS, Poulton R, Caspi A. 2016. The Genetics of Success: How Single-Nucleotide Polymorphisms Associated With Educational Attainment Relate to Life-Course Development. Psychol Sci. 27:957–972.

Berkson J. 1946. Limitations of the application of fourfold table analysis to hospital data. Biometrics. 2:27–53.

Bland JM, Altman DG. 2011. Statistics notes: Correlation in restricted ranges of data. BMJ. 343:577.

Brody GH, Gray JC, Yu T, Barton AW, Beach SRH, Galvan A, MacKillop J, Windle M, Chen E, Miller GE, Sweet LH. 2017. Protective prevention effects on the association of poverty with brain development. JAMA Pediatr. 171:46–52.

Burgess S, Scott RA, Timpson NJ, Smith GD, Thompson SG. 2015. Using published data in Mendelian randomization: A blueprint for efficient identification of causal risk factors. Eur J Epidemiol. 30:543–552.

Calvet G, Aguiar RS, Melo ASO, Sampaio SA, de Filippis I, Fabri A, Araujo ESM, de Sequeira PC, de Mendonça MCL, de Oliveira L, Tschoeke DA, Schrago CG, Thompson FL, Brasil P, dos Santos FB, Nogueira RMR, Tanuri A, de Filippis AMB. 2016. Detection and sequencing of Zika virus from amniotic fluid of fetuses with microcephaly in Brazil: a case study. Lancet Infect Dis. 16:653–660.

Cesarini D, Visscher PM. 2017. Genetics and educational attainment. npj Sci Learn. 2:4.

Deary IJ, Penke L, Johnson W. 2010. The neuroscience of human intelligence differences. Nat Rev Neurosci. 11.

DerSimonian R, Laird N. 1986. Meta-analysis in clinical trials. Control Clin Trials. 7:177–188.

Domingue BW, Belsky DW, Conley D, Harris KM, Boardman JD. 2015. Polygenic Influence on Educational Attainment. AERA Open. 1:1–13.

Dudbridge F. 2013. Power and Predictive Accuracy of Polygenic Risk Scores. PLoS Genet. 9:e1003348.

Elliott ML, Romer A, Knodt AR, Hariri AR. 2018. A Connectome-wide Functional Signature of Transdiagnostic Risk for Mental Illness. Biol Psychiatry. 1–8.
Falk EB, Hyde LW, Mitchell C, Faul J, Gonzalez R, Heitzeg MM, Keating DP, Langa KM, Martz ME, Maslowsky J, Morrison FJ, Noll DC, Patrick ME, Pfeffer FT, Reuter-Lorenz PA, Thomason ME, Davis-Kean P, Monk CS, Schulenberg J. 2013. What is a representative brain? Neuroscience meets population science. Proc Natl Acad Sci. 110:17615–17622.

Fischl B. 2012. FreeSurfer. Neuroimage.

Gignac GE, Bates TC. 2017. Brain volume and intelligence: The moderating role of intelligence measurement quality. Intelligence. 64:18–29.

Grotzinger AD, Rhemtulla M, Vlaming R de, Ritchie SJ, Mallard TT, Hill WD, Ip HF, McIntosh AM, Deary IJ, Koellinger PD, Harden KP, Nivard MG, Tucker-Drob EM. 2018. Genomic SEM Provides Insights into the Multivariate Genetic Architecture of Complex Traits. bioRxiv. 305029.

Haier RJ, Jung RE, Yeo RA, Head K, Alkire MT. 2004. Structural brain variation and general intelligence. Neuroimage. 23:425–433.

Hair NL, Hanson JL, Wolfe BL, Pollak SD. 2015. Association of child poverty, brain development, and academic achievement. JAMA Pediatr. 169:822–829.

Heckman JJ. 1979. Sample Selection Bias as a Specification Error. Econometrica. 47:153.

Holmes AJ, Hollinshead MO, O’Keefe TM, Petrov VI, Fariello GR, Wald LL, Fischl B, Rosen BR, Mair RW, Roffman JL, Smoller JW, Buckner RL. 2015. Brain Genomics Superstruct Project initial data release with structural, functional, and behavioral measures. Sci Data. 2.

Lewinn KZ, Sheridan MA, Keyes KM, Hamilton A, McLaughlin KA. 2017. Sample composition alters associations between age and brain structure. Nat Commun. 8.

Lyall DM, Cullen B, Allerhand M, Smith DJ, Mackay D, Evans J, Anderson J, Fawns-Ritchie C, McIntosh AM, Deary IJ, Pell JP. 2016. Cognitive test scores in UK biobank: Data reduction in 480,416 participants and longitudinal stability in 20,346 participants. PLoS One. 11.

Luby J, Belden A, Botteron K, Marrus N, Harms MP, Babb C, Nishino T, Barch D. 2013. The Effects of Poverty on Childhood Brain Development. JAMA Pediatr. 167:1135.

McDaniel MA. 2005. Big-brained people are smarter: A meta-analysis of the relationship between in vivo brain volume and intelligence. Intelligence. 33:337–346.

Mendoza JL, Mumford M. 1987. Corrections for Attenuation and Range Restriction on the Predictor. J Educ Stat. 12:282–293.

Miller KL, Alfaro-Almagro F, Bangerter NK, Thomas DL, Yacoub E, Xu J, Bartsch AJ, Jbabdi S, Sotiropoulos SN, Andersson JLR, Griffanti L, Douaud G, Okell TW, Weale P, Dragonu I, Garratt S, Hudson S, Collins R, Jenkinson M, Matthews PM, Smith SM. 2016. Multimodal population brain imaging in the UK Biobank prospective epidemiological study. Nat Neurosci. 19:1523.

Okbay A, Beauchamp JP, Fontana MA, Lee JJ, Pers TH, Rietveld CA, Turley P, Chen G-B, Emilsson V, Meddens SFW, Oskarsson S, Pickrell JK, Thom K, Timshel P, de Vlaming R, Abdellaoui A, Ahluwalia TS, Bacelis J, Baumbach C, Bjornsdottir G, Brandsma JH, Pina Concas M, Derringer J, Furlotte NA, Galesloot TE, Girotto G, Gupta R, Hall LM, Harris SE, Hofer E, Horikoshi M, Huffman JE, Kaasik K, Kalafati IP, Karlsson R, Kong A, Lahti J, Lee SJ van der, deLeeuw C, Lind PA, Lindgren K-O, Liu T, Mangino M, Marten J, Mihailov E, Miller MB, van der Most PJ, Oldmeadow C, Payton A, Pervjakova N, Peyrot WJ, Qian Y, Raitakari O, Ruedei R, Salvi E, Schmidt B, Schraut KE, Shi J, Smith A V.,
Poot RA, St Pourcain B, Teumer A, Thorleifsson G, Verweij N, Vuckovic D, Wellmann J, Westra H-J, Yang J, Zhao W, Zhu Z, Alizadeh BZ, Amin N, Bakshi A, Baumeister SE, Biino G, Bønnelykke K, Boyle PA, Campbell H, Cappuccio FP, Davies G, De Neve J-E, Deloukas P, Demuth I, Ding J, Eibich P, Eisele L, Eklund N, Evans DM, Faul JD, Feitosa MF, Forstner AJ, Gandin I, Gunnarsson B, Halldórsson B V., Harris TB, Heath AC, Hocking LJ, Holliday EG, Homuth G, Horan MA, Hottenga J-J, de Jager PL, Joshi PK, Jugessur A, Kaakinen MA, Kähönen M, Kanoni S, Keltigangas-Järvinen L, Kiemeney LALM, Kologic I, Koskinen S, Kraja AT, Kroh M, Kutalik Z, Latvala A, Launer LJ, Lebreton MP, Levinson DF, Lichtenstein P, Lichtner P, Liewald DCM, Cohort Study L, Loukola A, Madden PA, Mägi R, Mäki-Opas T, Marioni RE, Marques-Vidal P, Meddens GA, McMahon G, Meisinger C, Meitinger T, Milaneschi Y, Milani L, Montgomery GW, Myhre R, Nelson CP, Nyholt DR, Ollier WER, Palotie A, Paternoster L, Pedersen NL, Petrovic KE, Porteous DJ, Räikkönen K, Ring SM, Robino A, Rostapshova O, Rudan I, Rustichini A, Salomaa V, Sanders AR, Sarin A-P, Schmidt H, Scott RJ, Smith BH, Smith JA, Staessen JA, Steinhagen-Thiessen E, Strauch K, Terracciano A, Tobin MD, Ulivi S, Vaccargiu S, Quaye L, van Rooij FJA, Venturini C, Vinkhuyzen AAE, Völker U, Völzke H, Vonk JM, Vozzi D, Waage J, Ware EB, Willemsen G, Attia JR, Bennett DA, Berger K, Bertram L, Bisgaard H, Boomsma DI, Borecki IB, Bultmann U, Chabris CF, Cucca F, Cusi D, Deary IJ, Dedoussis G V., van Duijn CM, Eriksson JF, Franke B, Franke L, Gasparini P, Gejman P V., Gieger C, Grabe H-J, Gratten J, Groenewoud P, Gudnason V, van der Harst P, Hayward C, Hinds DA, Hoffmann W, Hyppönen E, Iacono WG, Jacobsen B, Järvelin M-R, Jöckel K-H, Kaprio J, Kardia SLR, Lehtimäki T, Lehrer SF, Magnuson PKE, Martin NG, McGue M, Metspalu A, Pendleton N, Penninx BWJH, Perola M, Pirastu N, Pirastu M, Polasek O, Posthuma D, Power C, Province MA, Samani NJ, Schlessinger D, Schmidt R, Sørensen TIA, Spector TD, Stefansson K, Thorsteindottir U, Thurik AR, Timpson NJ, Tiemeier H, Tung JY, Uitterlinden AG, Vitart V, Vollenweider P, Weir DR, Wilson JF, Wright AF, Conley DC, Krueger RF, Davey Smith G, Hofman A, Laibson DI, Medland SE, Meyer MN, Yang J, Johannesson M, Vischer PM, Esco T, Koellinger PD, Cesarini D, Benjamin DJ. 2016. Genome-wide association study identifies 74 loci associated with educational attainment. Nature. 533:539–542.

Peterson RA, Merunka DR. 2014. Convenience samples of college students and research reproducibility. J Bus Res. 67:1035–1041.

Pietschnig J, Penke L, Wicherts JM, Zeiler M, Voracek M. 2015. Meta-analysis of associations between human brain volume and intelligence differences: How strong are they and what do they mean? Neurosci Biobehav Rev. 57:411–432.

Plomin R, Deary IJ. 2015. Genetics and intelligence differences: five special findings. Mol Psychiatry. 20:98–108.

Plomin R, von Stumm S. 2018. The new genetics of intelligence. Nat Rev Genet.

Posthuma D, Baaré WFC, Pol HEH, Kahn RS, Boomsma DI, Geus EJC De. 2003. Genetic Correlations Between Brain Volumes and the WAIS-III Dimensions of Verbal Comprehension, Working Memory, Perceptual Organization, and Processing Speed. Twin Res Hum Genet. 6:131–139.

Posthuma D, De Geus EJC, Baaré WFC, Hulshoff Pol HE, Kahn RS, Boomsma DI. 2002. The association between brain volume and intelligence is of genetic origin. Nat Neurosci. 5:83–84.

Poulton R, Moffitt TE, Silva PA. 2015. The Dunedin Multidisciplinary Health and Development
Study: overview of the first 40 years, with an eye to the future. Soc Psychiatry Psychiatr Epidemiol.

Preacher KJ, Hayes AF. 2008. Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. Behav Res Methods. 40:879–891.

Price AL, N.j.patterson, R.m.plenge, M.e.weinblatt, N.a.shadick. 2006. Principal components analysis corrects for stratification in genome-wide association studies. Nat Genet. 38:904–909.

Rietveld CA, Esko T, Davies G, Pers TH, Turley P, Benyamin B, Chabris CF, Emilsson V, Johnson AD, Lee JJ, Leeuw C d., Marioni RE, Medland SE, Miller MB, Rostapshova O, van der Lee SJ, Vinkhuyzen AAE, Amin N, Conley D, Derringer J, van Duijn CM, Fehrmann R, Franke L, Glaeser EL, Hansell NK, Hayward C, Iacono WG, Ibrahim-Verbaas C, Jaddoe V, Karjalainen J, Lairdson D, Lichtenstein P, Liewald DC, Magnusson PKE, Martin NG, McGue M, McMahon G, Pedersen NL, Pinker S, Porteous DJ, Posthuma D, Rivadeneira F, Smith BH, Starr JM, Tiemeier H, Timpson NJ, Trzaskowski M, Uitterlinden AG, Verhulst FC, Ward ME, Wright MJ, Davey Smith G, Deary IJ, Johannesson M, Plomin R, Visscher PM, Benjamin DJ, Cesarini D, Koellinger PD. 2014. Common genetic variants associated with cognitive performance identified using the proxy-phenotype method. Proc Natl Acad Sci. 111:13790–13794.

Ritchie SJ, Tucker-Drob EM. 2018. How Much Does Education Improve Intelligence? A Meta-Analysis. Psychol Sci. 095679761877425.

Sears DO. 1986. College Sophomores in the Laboratory. Influences of a Narrow Data Base on Social Psychology’s View of Human Nature. J Pers Soc Psychol. 51:515–530.

Selzam S, Krapohl E, von Stumm S, O’Reilly PF, Rimfeld K, Kovas Y, Dale PS, Lee JJ, Plomin R. 2017. Predicting educational achievement from DNA. Mol Psychiatry. 22:267–272.

Smith SM, Zhang Y, Jenkinson M, Chen J, Matthews PM, Federico A, De Stefano N. 2002. Accurate, Robust, and Automated Longitudinal and Cross-Sectional Brain Change Analysis. Neuroimage. 17:479–489.

Sobel ME. 2007. Identification of Causal Parameters in Randomized Studies With Mediating Variables. J Educ Behav Stat. 33:230–251.

Stauffer JM, Mendoza JL. 2001. The proper sequence for correcting correlation coefficients for range restriction and unreliability. Psychometrika. 66:63–68.

Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, Downey P, Elliott P, Green J, Landray M, Liu B, Matthews P, Ong G, Pell J, Silman A, Young A, Sprosen T, Peckman T, Collins R. 2015. UK Biobank: An Open Access Resource for Identifying the Causes of a Wide Range of Complex Diseases of Middle and Old Age. PLoS Med. 12.

Tingley D, Yamamoto T, Hirose K, Keele L, Imai K. 2014. mediation: R Package for Causal Mediation Analysis. J Stat Softw. 59:1–38.

Toga AW, Thompson PM. 2005. Genetics of Brain Structure and Intelligence. Annu Rev Neurosci. 28:1–23.

Tucker-drob EM. 2017. Measurement Error Correction of Genome-Wide Polygenic Scores in Prediction Samples. bioRxiv.

van Valen L. 1974. Brain size and intelligence in man. Am J Phys Anthropol. 40:417–423.

Ware EB, Schmitz LL, Faul JD, Gard A, Mitchell C, Smith JA, Zhao W, Weir D, Kardia SL. 2017. Heterogeneity in polygenic scores for common human traits. bioRxiv. 106062.

Wechsler D. 1997. WAIS-III administration and scoring manual, The Psychological Corporation, San Antonio, TX.
Wechsler D. 2013. WASI -II: Wechsler abbreviated scale of intelligence - second edition. J Psychoeduc Assess. 31:337–341.
Wray NR, Goddard ME, Visscher PM. 2007. Prediction of individual genetic risk to disease from genome-wide association studies. Genome Res. 17:1520–1528.
Zachary RA. 1986. Shipley Institute of Living Scale: Revised Manual. Los Angeles East Psychol Serv.
### Tables

**Table 1. Samples and measures included in analysis.** Polygenic scores for all samples were computed based on the most recent GWAS of educational attainment (Okbay et al. 2016) following established methods.

| Sample                                                                 | Cognitive Test                                                                 | Total Brain Volume (cm³)                                                                 |
|------------------------------------------------------------------------|-------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| United Kingdom Biobank (UK Biobank) (Sudlow et al. 2015): An ongoing general population-based cohort of volunteers that was recruited from the UK National Health Service records beginning in 2006. | 13 verbal-numeric reasoning puzzles completed during a 2-minute time test (Lyall et al. 2016). Scored as number of correct responses. M = 6.97, SD = 2.10 | Total brain volume was derived from T1 weighted structural MRI images processed with Sienax (Smith et al. 2002) M = 1172.18, SD = 110.95 |
| N = 5691 54% female. Age M = 61.35, SD = 7.08                          |                                                                                |                                                                                        |
| Dunedin Multidisciplinary Health and Development Study (DMHDS) (Poulton et al. 2015): a population representative birth cohort born 1972-3 in Dunedin, New Zealand. Note: Here we report the available N, as of 2.2018, while data collection is ongoing. | Wechsler Adult Intelligence Scale-IV (WAIS-IV) (Wechsler 1997): Scored against a population norm with mean of 100 and standard deviation of 15. M = 100, SD = 15 | Total brain volume was derived from the recon-all pipeline in Freesurfer (Fischl 2012) using T1 and T2 weighted structural MRI images. M = 1224.48, SD = 124.19 |
| N = 596 52% female. Intelligence testing age = 38, MRI testing age = 45 |                                                                                |                                                                                        |
| Brain Genomics Superstruct Project (GSP) (Holmes et al. 2015): a convenience sample of Boston area healthy volunteers primarily recruited from local universities and medical centers. | Shipley Institute of Living Scale (Zachary 1986). Scored against a population norm with mean of 100 and standard deviation of 15. M = 113, SD = 9 | Total brain volume was derived from the recon-all pipeline in Freesurfer (Fischl 2012) using T1 and T2 weighted structural MRI images. M = 1174.58, SD = 110.64 |
| N = 1163 53% Female. Age M = 22.23, SD = 5.53                          |                                                                                |                                                                                        |
| Duke Neurogenetics Study (DNS): A convenience sample of university students primarily from Duke University. | Matrix reasoning and vocabulary subtests of the Wechsler Abbreviated Scale of Intelligence (Wechsler 2013) (WASI) Scored against a population norm with mean of 100 and standard deviation of 15. M = 124, SD = 7 | Total brain volume was derived from the recon-all pipeline in Freesurfer (Fischl 2012) using T1 weighted structural MRI images. M = 1162.40, SD = 110.34 |
Figures

| Study                  | Effect-Size   | %   |
|------------------------|---------------|-----|
| UK Biobank N=5,691     | 0.17          | 30.45 |
| Dunedin N=596          | 0.29          | 22.24 |
| GSP N=1,163            | 0.19          | 26.08 |
| DNS N=515              | 0.05          | 21.24 |
| Overall (I-squared = 82.5%, p = 0.001) | 0.17 | 100.00 |

NOTE: Weights are from random effects analysis

**Figure 1. Educational attainment polygenic score associations with cognitive test scores.** The figure shows a graph of effect-sizes for analyses of the UK Biobank, Dunedin Study (Dunedin), Brain Genomics Superstruct Project (GSP) and Duke Neurogenetics Study (DNS) samples (solid blue diamonds) and the cross-study effect-size estimated from random-effects meta-analysis (open blue diamond). Gray boxes around the solid-blue diamonds show the weighting of study-specific estimates in the meta-analysis (larger gray boxes indicate higher weights). 95% CIs for estimates are shown as error bars for the study-specific estimates and as the left- and right-extremes of the diamond for the meta-analysis effect-size. The meta-analysis estimate of between-study heterogeneity (I-squared) is listed to the left of the open blue diamond showing the meta-analysis effect-size. The table to the right of the effect-size graph reports values for effect-sizes, 95% CIs, and meta-analysis weights.
### Figure 2. Associations between brain size and cognitive test scores.

The figure shows a graph of effect-sizes for analyses of the UK Biobank, Dunedin Study (Dunedin), Brain Genomics Superstruct Project (GSP) and Duke Neurogenetics Study (DNS) samples (solid blue diamonds) and the cross-study effect-size estimated from random-effects meta-analysis (open blue diamond). Gray boxes around the solid-blue diamonds show the weighting of study-specific estimates in the meta-analysis (larger gray boxes indicate higher weights). 95% CIs for estimates are shown as error bars for the study-specific estimates and as the left- and right-extremes of the diamond for the meta-analysis effect-size. The meta-analysis estimate of between-study heterogeneity (I-squared) is listed to the left of the open blue diamond showing the meta-analysis effect-size. The table to the right of the effect-size graph reports values for effect-sizes, 95% CIs, and meta-analysis weights.
Figure 3. Educational attainment polygenic score associations with brain size. The figure shows a graph of effect-sizes for analyses of the UK Biobank, Dunedin Study (Dunedin), Brain Genomics Superstruct Project (GSP) and Duke Neurogenetics Study (DNS) samples (solid blue diamonds) and the cross-study effect-size estimated from random-effects meta-analysis (open blue diamond). Gray boxes around the solid-blue diamonds show the weighting of study-specific estimates in the meta-analysis (larger gray boxes indicate higher weights). 95% CIs for estimates are shown as error bars for the study-specific estimates and as the left- and right-extremes of the diamond for the meta-analysis effect-size. The meta-analysis estimate of between-study heterogeneity (I-squared) is listed to the left of the open blue diamond showing the meta-analysis effect-size. The table to the right of the effect-size graph reports values for effect-sizes, 95% CIs, and meta-analysis weights.
### Figure 4. Mediation effect of brain size on the association between the polygenic score for educational attainment and cognitive test scores

The figure shows a graph of effect-sizes for analyses of the UK Biobank, Dunedin Study (Dunedin), Brain Genomics Superstruct Project (GSP) and Duke Neurogenetics Study (DNS) samples (solid blue diamonds) and the cross-study effect-size estimated from random-effects meta-analysis (open blue diamond). Gray boxes around the solid-blue diamonds show the weighting of study-specific estimates in the meta-analysis (larger gray boxes indicate higher weights). 95% CIs for estimates are shown as error bars for the study-specific estimates and as the left- and right-extremes of the diamond for the meta-analysis effect-size. The meta-analysis estimate of between-study heterogeneity (I-squared) is listed to the left of the open blue diamond showing the meta-analysis effect-size. The table to the right of the effect-size graph reports values for effect-sizes, 95% CIs, and meta-analysis weights.

| Study                      | Effect Size | %   |
|----------------------------|-------------|-----|
| UK Biobank \( N=5,681 \)  | 0.01 (0.01, 0.02) | 34.32 |
| Dunedin \( N=596 \)       | 0.02 (0.00, 0.05)  | 11.30 |
| GSP \( N=1,163 \)         | 0.00 (-0.00, 0.01) | 32.45 |
| DNS \( N=515 \)           | 0.01 (-0.01, 0.02) | 21.93 |
| Overall (I-squared = 78.9%, \( p = 0.003 \)) | 0.01 (0.00, 0.02) | 100.00 |

**NOTE:** Weights are from random effects analysis.