Supplementary Materials for:

Hagenaars et al. Shared genetic aetiology between cognitive functions and physical and mental health in UK Biobank (N = 112 151) and 24 GWAS consortia

Contents

Supplementary Table 1
For each health-related phenotype for which we use genome-wide association study summary data, here are some key example references showing its relation to prior cognitive function (left-hand column) and its possible effects on later cognitive function (right-hand column). (-) indicates a negative association with cognitive function, while (+) indicates a positive association with cognitive function.

Link to prior cognitive function	Phenotype	Effect on cognitive function
	Vascular-metabolic diseases	
Lawlor et al. (2008). (-)	Coronary Artery Disease	Kovacic et al. (2012) (-) Eggermont et al (2012) (-)
Lawlor et al. (2008) (-) Rajan et al. (2014) (-)	Stroke: Ischaemic	Brainin et al. (2015) (-)
Lawlor et al. (2008) (-) Rajan et al. (2014) (-)	Stroke: Cardioembolic	Brainin et al. (2015) (-)
Lawlor et al. (2008) (-) Rajan et al. (2014) (-)	Stroke: Large Vessel Disease	Brainin et al. (2015) (-)
Lawlor et al. (2008) (-) Rajan et al. (2014) (-)	Stroke: Small Vessel Disease	Brainin et al. (2015) (-)
Mõttus et al. (2013) (-)	Type 2 Diabetes	Rawlings et al. (2014) (-)
	Neuropsychiatric disorders	
N/A	ADHD	Frazier et al. (2004) (-)
Whalley et al. (2000) (-)	Alzheimer's Disease	N/A
N/A	Autism	Fombonne et al. (2005) (-)
Gale et al. (2013) (+)	Bipolar Disorder	Gildengers et al. (2009) (-)
Gale et al. (2008) (-)	Major Depressive Disorder	Wilson et al. (2014) (-)
Dickson et al. (2012) (-)	Schizophrenia	Hedman et al. (2013) (-)
	Brain measures	
Aribisala et al. (2014) (+)	Hippocampal Volume	van Petten et al. (2004)
Royle et al. (2013) (+)	Intracranial Volume	Pietschnig et al. (2014) (+)
N/A	Infant Head Circumference	Gale et al. (2003) (+)
	Physical and physiological measures	
Starr et al. (2004) (-)	Blood Pressure: Diastolic	Taylor et al. (2013) (+/-) Novak & Hajjar (2010) (+/-)
Starr et al. (2004) (-)	Blood Pressure: Systolic	Gottesman et al. (2014) (-) Novak & Hajjar (2010) (+/-)
Belsky et al. (2013) (-)	BMI	Dahl et al. (2010) (-)
No reference found.	Height	Russ et al. (2014) (+)
Calvin et al. (2011) (+)	Longevity	N/A
Richards et al. (2005) (+)	Forced Expiratory Volume in 1s	Emery et al. (2012) (+)
	Life-course Cognitive traits and proxies	
N/A	Childhood cognitive ability	Deary et al. (2013) (+)
Strenze (2007) (+)	College degree	Clouston et al. (2012) (+)
Strenze (2007) (+)	Years of Education	Banks & Mazzonna (2012) (+)

References for Supplementary Table 1

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Descriptions of Cognitive Phenotypes

Reaction Time Test
Reaction Time (RT) was measured in all participants using a computer-based 'Snap' game, conceptually similar to some 'Go/No-Go' reaction time tasks. Two cards with simple symbols (e.g. a square or equals sign), were presented to participants on a computer screen. Participants were instructed to push an adjacent button box as quickly as possible, using their dominant hand, if the two cards had identical symbols. After completing four practice trials, participants completed eight experimental trials, of which four included identical pairs; these four required a button to be pressed. Each participant's RT score was calculated as the mean time (in ms) to push the button for the four trials in which the stimuli were identical. Owing to a positively-skewed distribution, the reaction time data were log-transformed before analysis. One participant with an outlying reaction time score (1905 ms, which is over 11 standard deviations above the mean RT) had their data removed from the analysis. The Cronbach alpha coefficient, which provides an internal consistency type of reliability, for the five trials was 0.85. The UK Biobank Field IDs used in this test were 401, 402, 403, and 404. There is a linear decline in mean performance (with longer reaction times found) between age 40 and 70 years (Supplementary Figure 1, below).

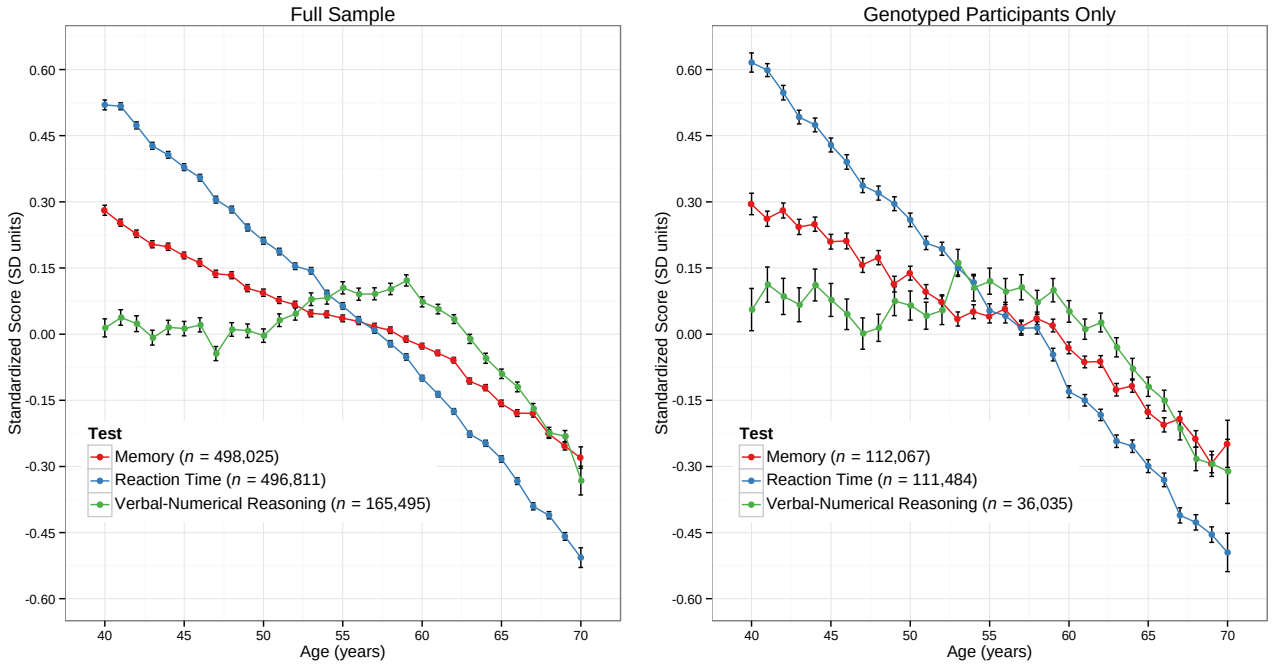
Memory (Pairs Matching) Test
Memory was measured using a computerised 'pairs matching' game. There were two rounds of the game. In the first round, three pairs of cards with matching simple symbols, arranged randomly in a grid, were presented to participants on a computer screen for three seconds. The cards were then 'turned' face down. The participants were instructed to select, from recall and in the fewest number of attempts, the pairs of cards that had matching symbols. Pairs were identified by the participant's touching identical cards on the screen consecutively. There was no time limit and the participants could make as many attempts as they needed to find all the pairs. The second round included six pairs of cards, shown for five seconds. Only the results from this second, more challenging round of the memory test were used in this study. The memory test score in the present study is the total number of errors made during this task until the six pairs of identical cards were touched consecutively. Twenty-nine participants who made more than 30 errors on the task had their number of errors set to 30 (this was not performed for the GWAS analysis, therefore this does not apply to the LD regression analysis). The UK Biobank field ID for the variable used here (number of errors in the second round) was 399. There is a linear decline in mean performance (more errors) between age 40 and 70 years (Supplementary Figure 1, below).

Verbal-numerical Reasoning Test
This test is named 'fluid intelligence' in UK Biobank. This verbal-numerical reasoning test comprised thirteen questions presented serially on a computer screen. There were six verbal items. There were seven numerical items, involving sequence recognition and arithmetic. Participants were required to answer all the items within two minutes. All were multiple-choice. An example verbal item is: "Age is to years as height is to?" (answer options were, "Long/Deep/Top/Metres/Tall/Do not know/Prefer not to answer"). An example numerical item is: "150…137…125…114…104… what comes next?" (answer options were, "96/95/94/93/92/Do not know/Prefer not to answer"). The total score out of thirteen was recorded and used for the present study. The Cronbach alpha coefficient for the thirteen items was 0.62. The UK Biobank Field IDs (variable names) used in this test, with each one corresponding to each of the 13 items, were 4935, 4946, 4957, 4968, 4979, 4990, 5001, 5012, 5556, 5699, 5779, 5790, and 5866. The scores on this test show stable mean values between age 40 and 60 years, and linear decline in mean scores between age 60 and 70 years (Supplementary Figure 1, below). Therefore, this test does not, across the whole age range, show the characteristic age-related decline expected from 'fluid' cognitive functions—the name the test has in UK Biobank—and so we refer to the test by its content, which is verbal-numerical reasoning. The cross-sectional age-related pattern of this test is similar to that shown by vocabulary tests, which are used to assess crystallised cognitive ability (Salthouse TA, Localizing age-related individual differences in a hierarchical structure. Intelligence; 32, 541-561, Figure 3).

Educational Attainment
As part of the sociodemographic questionnaire in the study, participants were asked, "Which of the following qualifications do you have? (You can select more than one)". Possible answers were: "College or University Degree/A levels or AS levels or equivalent/O levels or GCSE or equivalent/CSEs or equivalent/NVQ or HND or HNC or equivalent/Other professional qualifications e.g. nursing, teaching/None of the above/Prefer not to answer". For the present study, a binary education variable was created to indicate whether or not a participant had a college or university-level degree. This educational attainment variable was used in this study as what has been named and validated as a 'proxy phenotype' for cognitive function (Rietveld CA, Esko T, Davies G, et al. Common genetic variants associated with cognitive performance identified using the proxy-phenotype method. Proc Natl Acad Sci 2014; 111: 13790-13794).

Supplementary Figure 1

Age trends in standardized mean scores for the three cognitive abilities (Memory, Reaction Time, and Verbal-Numerical Reasoning) in the full sample (left) and the participants with genotyping data available (right). Error bars represent +/- one standard error of the mean. Valid sample sizes are shown for each individual test. Memory and Reaction Time tests had scores reversed so that lower scores indicate poorer performance for all three tests. For the 'Full Sample' figure, six participants aged under 40 years and seven participants aged over 70 years were removed. For the 'Genotyped Participants Only' figure, one participant aged over 70 years was removed.



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Genotyping and Quality Control

Genotyping was performed on 33 batches of ~4700 samples by Affymetrix, who also performed initial quality control of the genotyping data. Further details are available of the sample processing specific to the UK Biobank project (http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=155583) and the Axiom array (http://media.affymetrix.com/support/downloads/manuals/axiom_2_assay_auto_workflow_user_guide.pdf). Prior to the release of the UK Biobank genetic data a stringent QC protocol was applied, and performed at the Wellcome Trust Centre for Human Genetics (WTCHG); details of this process can be found at the following URL (http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=155580).

Prior to the analyses described in the main report, further quality control measures were applied by the present authors. Individuals were removed based on missingness, relatedness (KING estimated kinship co-efficient > 0.0442), gender mismatch, non-British ancestry (principal component analysis identified probable Caucasians within those individuals that were self-identified as British), and QC failure in the UK Bileve study. A sample of 112 151 individuals remained for further analyses. A minor allele frequency of maf < 1% filter was applied and only autosomal variants were used in this study (N = 705 516).

Genome-wide association analyses (GWAS) in the UK Biobank sample

An imputed dataset, including >70 million variants, was made available in which the UK Biobank interim release was imputed to a reference set which combined the UK10K haplotype and 1000 Genomes Phase 3 reference panels. Further details can be found at the following URL: http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=157020. Genome-wide association analyses were performed on the imputed dataset using SNPTest v2.5.1 (Marchini J, Howie B, Myers S, et al. A new multipoint method for genome-wide association studies via imputation of genotypes. Nat Genet 2007; 39: 906-913; SNPTEST v.2.5.1 can be found at the following URL: https://mathgen.stats.ox.ac.uk/genetics_software/snptest/snptest.html#introduction). An additive model was specified using the "frequentist 1" option. To account for genotype uncertainty we analysed the expected genotyped counts (dosages). Adjustments for age, sex, genotyping batch, genotyping array, assessment centre and 10 principal components were included. Prior to use in LD regression analyses the association results were filtered based on minor allele frequency (<0.1%) and imputation quality (<0.1).

Sources of genetic results from genome-wide association consortia

CARDIoGRAM
Coronary artery disease data have been contributed by CARDIoGRAMplusC4D investigators.

CHARGE-Aging and Longevity
Longevity data have been provided by the CHARGE-Aging and Longevity consortium. Longevity was defined as reaching age 90 years or older. Genotyped participants who died between the ages of 55 and 80 years were used as the control group. There were 6036 participants who achieved longevity and 3757 participants in the control group across participating studies in the discovery meta-analysis.

Broer L, Buchman AS, Deelen J, Evans DS, Faul JD, Lunetta KL, Sebastiani P, Smith JA, Smith AV, Tanaka T, Yu L, Arnold AM, Aspelund T, Benjamin EJ, De Jager PL, Eirkisdottir G, Evans DA, Garcia ME, Hofman A, Kaplan RC, Kardia SL, Kiel DP, Oostra BA, Orwoll ES, Parimi N, Psaty BM, Rivadeneira F, Rotter JI, Seshadri S, Singleton A, Tiemeier H, Uitterlinden AG, Zhao W, Bandinelli S, Bennett DA, Ferrucci L, Gudnason V, Harris TB, Karasik D, Launer LJ, Perls TT, Slagboom PE, Tranah GJ, Weir DR, Newman AB, van Duijn CM and Murabito JM. **GWAS of Longevity in CHARGE Consortium Confirms APOE and FOXO3 Candidacy**. *J Gerontol A Biol Sci Med Sci*. 2015;70:110-8.

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DIAGRAM
Type 2 diabetes data were obtained from the DIAGRAM consortium.

International Consortium of Blood Pressure (ICBP)
Blood pressure data were provided by ICBP.

Early Growth Genetics Consortium (EGG)
Head circumference data has been contributed by the EGG Consortium.

ENIGMA
Brain imaging data were obtained from the ENIGMA consortium.

GIANT
Height and BMI data were obtained from the GIANT consortium.

International Genomics of Alzheimer's Project (IGAP)
Alzheimer's disease data were obtained from (IGAP)
Material and methods
International Genomics of Alzheimer's Project (IGAP) is a large two-stage study based upon genome-wide association studies (GWAS) on individuals of European ancestry. In stage 1, IGAP used genotyped and imputed data on 7 055 881 single nucleotide polymorphisms (SNPs) to meta-analyse four previously-published GWAS datasets consisting of 17 008 Alzheimer's disease cases and 37 154 controls (The European Alzheimer's disease Initiative – EADI the Alzheimer Disease Genetics Consortium – ADGC The Cohorts for Heart and Aging Research in Genomic Epidemiology consortium – CHARGE The Genetic and Environmental Risk in AD consortium – GERAD). In stage 2, 11 632 SNPs were genotyped and tested for association in an independent set of 8572 Alzheimer's disease cases and 11 312 controls. Finally, a meta-analysis was performed combining results from stages 1 & 2.

Acknowledgments
We thank the International Genomics of Alzheimer's Project (IGAP) for providing summary results data for these analyses. The investigators within IGAP contributed to the design and implementation of IGAP and/or provided data but did not participate in analysis or writing of this report. IGAP was made possible by the generous participation of the control subjects, the patients, and their families. The i–Select chips was funded by the French National Foundation on Alzheimer's disease and related disorders. EADI was supported by the LABEX (laboratory of excellence program investment for the future) DISTALZ grant, Inserm, Institut Pasteur de Lille, Université de Lille 2 and the Lille University Hospital. GERAD was supported by the Medical Research Council (Grant n° 503480), Alzheimer's Research UK (Grant n° 503176), the Wellcome Trust (Grant

n° 082604/2/07/Z) and German Federal Ministry of Education and Research (BMBF): Competence Network Dementia (CND) grant n° 01GI0102, 01GI0711, 01GI0420. CHARGE was partly supported by the NIH/NIA grant R01 AG033193 and the NIA AG081220 and AGES contract N01–AG–12100, the NHLBI grant R01 HL105756, the Icelandic Heart Association, and the Erasmus Medical Center and Erasmus University. ADGC was supported by the NIH/NIA grants: U01 AG032984, U24 AG021886, U01 AG016976, and the Alzheimer's Association grant ADGC–10–196728.

METASTROKE

Ischaemic stroke data were obtained from the METASTROKE consortium. The METASTROKE consortium is supported by NINDS (NS017950). We thank all study participants, volunteers, and study personnel that made this consortium possible. The METASTROKE study consists of combined data from 15 GWAS of IS (12 389 cases vs 62 004 controls). We used TOAST criteria17 to classify IS as large artery stroke (LAS) (2167 cases/49 159 controls from 11 studies), cardioembolic stroke (CE) (2365 cases/ 56,140 controls from 13 studies), and small vessel disease (SVD) (1894 cases/51 976 controls from 12 studies). METASTROKE studies consisted of independently performed genome-wide single nucleotide polymorphism (SNP) genotyping using standard technologies and imputation to HapMap release 21 or 22 CEU phased genotype18 or 1000 Genome reference panels. Investigators contributed summary statistical data from association analyses using frequentist additive models for metaanalysis after application of appropriate quality control measures. Polygenic scores reveal combined effects of multiple nonsignificant variants derived from a derivation sample and tested in an independent replication sample. We derived polygenic scores for multiple p value cutoffs (0.5, 0.25, 0.1, 0.05, 0.01, 0.001, and 0.0001) in derivation samples.

Psychiatric Genetics Consortium

Schizophrenia, bipolar disorder, major depressive disorder, ADHD and autism data were obtained from the Psychiatric Genetics Consortium.

Social Science Genetic Association Consortium

Years of education, college degree and childhood cognitive ability data were obtained from the Social Science Genetic Association Consortium.

SpiroMeta/CHARGE-Pulmonary

Lung function data were obtained from the SpiroMeta and CHARGE-Pulmonary consortia.

Supplementary Table 2

Sources of genetic results from genome-wide association consortia.

Phenotype	Consortium	URL	Reference	No. of individuals in GWAS
Coronary Artery Disease	CARDIoGRAM	http://www.cardiogramplusc4d.org/downloads/	Schunkert et al. Nat Genet 2011; 43: 333-338. PMID: 21378990	22 233 cases 64 762 controls
Stroke:Ischaemic	METASTROKE	http://www.strokegenetics.com/members-area/meta-stroke	Traylor et al. Lancet Neurol 2012; 11: 951-962. PMID: 23041239	12 389 cases 62,004 controls
Stroke: Cardioembolic	METASTROKE	http://www.strokegenetics.com/members-area/meta-stroke	Traylor et al. Lancet Neurol 2012; 11: 951-962. PMID: 23041239	2365 cases 62 004 controls
Stroke: Large-vessel disease	METASTROKE	http://www.strokegenetics.com/members-area/meta-stroke	Traylor et al. Lancet Neurol 2012; 11: 951-962. PMID: 23041239	2167 cases 62 004 controls
Stroke: Small-vessel disease	METASTROKE	http://www.strokegenetics.com/members-area/meta-stroke	Traylor et al. Lancet Neurol 2012; 11: 951-962. PMID: 23041239	1894 cases 62 004 controls
Type 2 diabetes	DIAGRAM	http://diagram-consortium.org/downloads.html	Morris et al. Nat Genet 2012; 44: 981-990. PMID: 22885922	12 171 cases 56 862 controls
ADHD	Psychiatric Genetics Consortium (PGC)	https://www.med.unc.edu/pgc/downloads	Cross-Disorder Group of the Psychiatric Genomics Consortium. Lancet 2013; 381: 1371-1379. PMID: 23453885	1947 trio cases 1947 trio pseudocontrols, 840 cases 688 controls
Alzheimer's disease	International Genomics of Alzheimer's Project (IGAP)	http://www.pasteur-lille.fr/en/recherche/u744/igap/igap_download.php	Lambert et al. Nat Genet 2013; 45: 1452-1458. PMID: 24162737	17 008 cases 37 154 controls
Autism	Psychiatric Genetics Consortium (PGC)	https://www.med.unc.edu/pgc/downloads	Cross-Disorder Group of the Psychiatric Genomics Consortium. Nat Genet 2013: 45; 984-994. PMID: 23933821	3303 cases 3428 controls
Bipolar disorder	Psychiatric Genetics Consortium (PGC)	https://www.med.unc.edu/pgc/downloads	Psychiatric GWAS Consortium Bipolar Disorder Working Group. Nat Genet 2011; 43: 977-983. PMID: 21926972	7481 cases 9250 controls
Major depressive disorder	Psychiatric Genetics Consortium (PGC)	https://www.med.unc.edu/pgc/downloads	Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium. Mol Psychiatr 2013; 18: 497-511. PMID: 22472876	9240 cases 9519 controls
Schizophrenia	Psychiatric Genetics Consortium (PGC)	https://www.med.unc.edu/pgc/downloads	Schizophrenia Working Group of the Psychiatric Genomics Consortium. Nature 2014; 511: 421-427. PMID: 25056061	36 989 cases 113 075 controls
Hippocampal volume	ENIGMA	http://enigma.ini.usc.edu/ongoing/gwas ma-of-subcorticalstructures/	Hibar et al. Nature 2015; 520: 224-229. PMID: 25607358	13 171
Intracranial volume	ENIGMA	http://enigma.ini.usc.edu/ongoing/gwas ma-of-subcorticalstructures/	Hibar et al. Nature 2015; 520: 224-229. PMID: 25607358	13 171
BMI	GIANT	http://www.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files	Locke et al. Nature 2015; 518: 197-206. PMID: 25673413	339 224
Diastolic blood pressure	International Consortium of Blood Pressure (ICBP)		Ehret et al. (2011) Nature 478, 103-109. PMID: 21909115	69 395
Height	GIANT	http://www.broadinstitute.org/collaborati	Wood et al. Nat Genet 2014; 11: 1173-86. PMID: 25282103	253 288

		on/ giant/index.php/GIANT_ consortium_data_files		
Infant head circumference	Early Growth Genetics Consortium	http://egg-consortium.org/head-circumference.html	Taal et al. Nat Genet 2012; 15: 532-538. PMID: 22504419	10 768
Longevity	CHARGE-Aging and Longevity		Broer et al. J Gerontol A Biol Sci Med Sci 2015; 70: 110-118. PMID: 25199915	6036 cases 3757 controls
Forced expiratory volume in 1 second (FEV1)	SpiroMeta/CHARGE-Pulmonary		Soler Artigas et al. Nature Genetics 2011; 43: 1082-1090. PMID: 21946350	48 201
Systolic blood pressure	International Consortium of Blood Pressure (ICBP)		Ehret et al. Nature 2011; 478: 103-109. PMID: 21909115	69 395
Childhood cognitive ability	Social Science Genetic Association Consortium	http://ssgac.org/Data.php	Benyamin et al. Mol Psychiatr 2014; 19: 253-258. PMID: 23358156	17 989
College degree	Social Science Genetic Association Consortium	http://ssgac.org/Data.php	Rietveld et al. Science 2013; 314: 1467-1471. PMID: 23722424	95 427
Years of Education	Social Science Genetic Association Consortium	http://ssgac.org/Data.php	Rietveld et al. Science 2013; 314: 1467-1471. PMID: 23722424	101 069

LD regression genetic correlation procedure

The patterns of LD found across the genome enable genetic correlations between traits to be derived. This is due to two reasons. Firstly, the level of association a SNP shows in a GWAS is a product of both its own contribution toward a phenotype and those that are in LD with it (Yang J, Weedon MN, Purcell S, et al. Genomic inflation factors under polygenic inheritance. Eur J Hum Genet 2011;19: 807-812). Additionally, SNPs in regions of high LD tag a greater proportion of the genome than SNPs in regions of low LD. These two facts mean that, assuming a polygenic architecture, SNPs in regions of high LD will have greater association statistics than SNPs found in regions of low LD. The effect of this is that GWAS association test statistics can be predicted using LD (Bulik-Sullivan B, Finucane HK, Anttila V et al. An atlas of genetic correlations across human diseases and traits. bioRxiv 2015; doi: http://dx.doi.org/10.1101/014498). This logic can also be extended to a bivariate design, where LD can be used to predict the product of pairs of test statistics for each locus across GWAS datasets (Bulik-Sullivan B, Loh PR, Finucane H, et al. LD score regression distinguishes confounding from polygenicity in genome-wide association studies. Nat Genet 2015; 47: 291-295).

We followed the protocol of the above studies by Bulik-Sullivan et al., where data sets demonstrating a heritability Z-score (h^2_z) > 4 and a mean χ^2 statistic of > 1.02 were included. All traits, except small vessel disease exceeded these thresholds. This threshold was implemented in order to establish that each GWAS data set had evidence of a clear polygenic signal. Where it was included in the summary statistics provided, a MAF of > 0.01 was used as a cut off. To control for imputation quality, only those SNPs found in the HapMap3 with 1000 Genomes EUR with a MAF > 0.05 were included (integrated_phase1_v3.20101123). Next, indels and structural variants were removed along with strand-ambiguous SNPs. Finally, genome-wide significant SNPs were removed, as were SNPs with very large effect sizes (χ^2 > 80), as the presence of outliers can increase the standard error in a regression model. LD scores and weights for use with the GWAS of European ancestry were downloaded from the Broad institute (http://www.broadinstitute.org/~bulik/eur_ldscores/). An unconstrained intercept was used in the regression model as it was not possible to quantify the degree of sample overlap between the traits used here.

Polygenic profiling procedure

The genetic data files (.map and .ped files) supplied from Biota (the UK Biobank online repository) were unsuitable for use in the polygenic profile analyses as the .ped allele coding used a 1, 2 numeric allele encode rather than the standard ACGT encode format. In order to enable the analysis, the .ped files were recoded to the standard encode format. To achieve this, a bespoke programme was developed to create new files using a lookup-substitution method. A fast-in-memory lookup string hash table was created to hold the SNP-ID, along with the allele identifiers for the SNP. A simple loop then performed serialised lookups based on string position, to create an associated string with the correct ACGT encode. This was then appended to the six mandatory data fields extracted from initial string. In order to maximise performance and enable timely completion of the lookup-substitution, these loops were run in parallel threads in a standard multiprocessor environment.

Sensitivity analysis

To test whether FDR significant associations between polygenic risk for coronary artery disease, and Verbal-numerical reasoning and educational attainment were confounded by individuals diagnosed with cardiovascular disease, 2779 individuals who had had a heart attack and 2521 individuals with angina were removed from the regression analysis. Similarly 5800 individuals with diabetes (type 1 or type 2) were removed from the regression investigating an association between polygenic risk for type 2 diabetes and educational attainment. Finally, 26 912 individuals with hypertension were removed from the regression analysis investigating the association between polygenic risk for systolic blood pressure and educational attainment.

Supplementary Table 3

Number of SNPs included at each threshold for the polygenic profile scores.

		Threshold	Number of SNPs
Vascular-Metabolic Diseases	Coronary Artery Disease	0.01	2633
		0.05	9981
		0.1	18159
		0.5	72443
		1	121718
	Stroke: Ischaemic	0.01	3006
		0.05	13448
		0.1	25588
		0.5	105309
		1	173745
	Stroke: Cardioembolic	0.01	2885
		0.05	13295
		0.1	25366
		0.5	104731
		1	172809
	Stroke: Large Vessel Disease	0.01	2915
		0.05	13354
		0.1	25243
		0.5	104188
		1	172973
	Stroke: Small Vessel Disease	0.01	2853
		0.05	13116
		0.1	25303
		0.5	104042
		1	172697
	Type 2 Diabetes	0.01	2461
		0.05	9969
		0.1	18172
		0.5	73505
		1	124964
Neuro-Psychiatric Disorders	ADHD	0.01	1394
		0.05	6357
		0.1	12305
		0.5	55047
		1	98438
	Alzheimer's Disease	0.01	5030
		0.05	20437
		0.1	37843
		0.5	152714
		1	254358
	Autism	0.01	4736
		0.05	22299
		0.1	43182

		0.5	192694
		1	334262
	Bipolar Disorder	0.01	2625
		0.05	10418
		0.1	18907
		0.5	75289
		1	127481
	Major Depressive Disorder	0.01	1532
		0.05	6878
		0.1	12995
		0.5	56175
		1	98450
	Schizophrenia	0.01	12006
		0.05	35598
		0.1	58837
		0.5	194510
		1	310629
Brain Measures	Hippocampal Volume	0.01	3954
		0.05	17974
		0.1	34469
		0.5	148964
		1	252716
	Intracranial Volume	0.01	4046
		0.05	18683
		0.1	35510
		0.5	150389
		1	253355
	Infant Head Circumference	0.01	2031
		0.05	9004
		0.1	16994
		0.5	73859
		1	127665
Physical and physiological measures	Blood Pressure: Diastolic	0.01	1952
		0.05	8535
		0.1	16298
		0.5	74773
		1	133754
	Blood Pressure: Systolic	0.01	1961
		0.05	8379
		0.1	16253
		0.5	74616
		1	133823
	BMI	0.01	2612
		0.05	8503
		0.1	15648
		0.5	72010
		1	131142
	Height	0.01	11360
		0.05	23651

		0.1	34188
		0.5	86984
		1	131070
	Longevity	0.01	2023
		0.05	9292
		0.1	17646
		0.5	77146
		1	133920
	Forced Expiratory Volume in 1s (FEV_1)	0.01	1963
		0.05	8677
		0.1	16794
		0.5	76920
		1	136779
Life-course Cognitive Traits and Proxies	Childhood Cognitive Ability	0.01	1187
		0.05	4945
		0.1	9069
		0.5	37967
		1	65356
	College degree	0.01	2715
		0.05	10076
		0.1	17650
		0.5	66808
		1	109983
	Years of Education	0.01	2702
		0.05	9886
		0.1	17577
		0.5	65990
		1	108127

Supplementary Table 4a

Associations between polygenic profiles of health related traits, and verbal-numerical reasoning controlling for age, sex, assessment centre, genotyping batch and array, and ten principal components for population structure. Statistically significant values (P<0.0188) are shown in bold. Cognitive/education phenotypes are scored such that higher scores indicate better performance.

Trait category	Trait	Verbal-Numerical Reasoning				
		Threshold	β	SE	R2	P
Vascular-Metabolic Diseases	Coronary Artery Disease	0.01	−0.017	0.0052	0.0003	**0.0009**
		0.05	−0.012	0.0052	0.0002	0.0188
		0.1	−0.011	0.0052	0.0001	0.0393
		0.5	−0.019	0.0052	0.0004	**0.0002**
		1	−0.018	0.0052	0.0003	**0.0005**
	Stroke: Ischaemic	0.01	−0.010	0.0053	0.0001	0.0474
		0.05	−0.014	0.0053	0.0002	**0.0068**
		0.1	−0.006	0.0053	3.47×10^{-5}	0.2604
		0.5	−0.007	0.0053	4.42×10^{-5}	0.2041
		1	−0.003	0.0053	1.02×10^{-5}	0.5428
	Stroke: Cardioembolic	0.01	0.005	0.0052	2.45×10^{-5}	0.3444
		0.05	0.000	0.0052	8.40×10^{-8}	0.9558
		0.1	−0.005	0.0052	2.06×10^{-5}	0.3858
		0.5	−0.008	0.0052	0.0001	0.1092
		1	−0.009	0.0052	0.0001	0.0937
	Stroke: Large Vessel Disease	0.01	−0.013	0.0053	0.0002	**0.0155**
		0.05	−0.004	0.0053	1.28×10^{-5}	0.4948
		0.1	−0.007	0.0053	4.24×10^{-5}	0.2134
		0.5	−0.002	0.0052	4.11×10^{-6}	0.6986
		1	−0.010	0.0052	0.0001	0.0629
	Stroke: Small Vessel Disease	0.01	−0.005	0.0052	2.99×10^{-5}	0.2962
		0.05	−0.012	0.0053	0.0001	0.0250
		0.1	−0.007	0.0053	4.34×10^{-5}	0.2085
		0.5	0.001	0.0052	8.21×10^{-7}	0.8626
		1	0.001	0.0052	1.26×10^{-6}	0.8300
	Type 2 Diabetes	0.01	−0.002	0.0053	5.84×10^{-6}	0.6446
		0.05	−0.001	0.0053	1.63×10^{-6}	0.8073
		0.1	−0.004	0.0053	1.60×10^{-5}	0.4442
		0.5	−0.006	0.0054	2.98×10^{-5}	0.2969
		1	−0.006	0.0054	3.64×10^{-5}	0.2490
Neuro-Psychiatric Disorders	ADHD	0.01	−0.002	0.0052	5.74×10^{-6}	0.6474
		0.05	−0.001	0.0052	3.12×10^{-7}	0.9150
		0.1	−0.004	0.0052	1.67×10^{-5}	0.4354
		0.5	−0.007	0.0052	0.0001	0.1597
		1	−0.008	0.0052	0.0001	0.1054
	Alzheimer's Disease	0.01	−0.014	0.0052	0.0002	**0.0061**
		0.05	−0.023	0.0053	0.0005	**1.27×10^{-5}**
		0.1	−0.023	0.0053	0.0005	**1.34×10^{-5}**
		0.5	−0.021	0.0053	0.0004	**0.0001**
		1	−0.022	0.0053	0.0005	**3.97×10^{-5}**
	Autism	0.01	0.016	0.0052	0.0003	**0.0023**

		0.05	0.016	0.0052	0.0002	**0.0028**
		0.1	0.019	0.0052	0.0003	**0.0004**
		0.5	0.022	0.0052	0.0005	**1.92×10^{-5}**
		1	0.023	0.0052	0.0005	**1.43×10^{-5}**
	Bipolar Disorder	0.01	−0.006	0.0052	3.34×10^{-5}	0.2695
		0.05	−0.003	0.0053	7.87×10^{-6}	0.5920
		0.1	−0.003	0.0053	1.01×10^{-5}	0.5433
		0.5	−0.004	0.0053	1.24×10^{-5}	0.5006
		1	−0.004	0.0053	1.59×10^{-5}	0.4463
	Major Depressive Disorder	0.01	−0.008	0.0053	0.0001	0.1455
		0.05	−0.008	0.0053	0.0001	0.1366
		0.1	−0.014	0.0053	0.0002	**0.0071**
		0.5	−0.018	0.0053	0.0003	**0.0005**
		1	−0.020	0.0053	0.0004	**0.0002**
	Schizophrenia	0.01	−0.055	0.0053	0.0030	**2.04×10^{-25}**
		0.05	−0.062	0.0053	0.0038	**7.73×10^{-32}**
		0.1	−0.062	0.0053	0.0037	**3.22×10^{-31}**
		0.5	−0.062	0.0054	0.0037	**2.59×10^{-31}**
		1	−0.062	0.0054	0.0036	**1.34×10^{-30}**
Brain Measures	Hippocampal Volume	0.01	0.005	0.0052	2.34×10^{-5}	0.3552
		0.05	0.000	0.0052	1.05×10^{-8}	0.9844
		0.1	−0.002	0.0052	4.24×10^{-6}	0.6943
		0.5	0.002	0.0052	2.78×10^{-6}	0.7500
		1	−0.001	0.0052	3.26×10^{-7}	0.9132
	Intracranial Volume	0.01	0.013	0.0053	0.0002	**0.0113**
		0.05	0.009	0.0053	0.0001	0.0895
		0.1	0.013	0.0053	0.0002	**0.0140**
		0.5	0.016	0.0054	0.0003	**0.0021**
		1	0.016	0.0054	0.0003	**0.0023**
	Infant Head Circumference	0.01	0.019	0.0052	0.0003	**0.0004**
		0.05	0.019	0.0053	0.0003	**0.0004**
		0.1	0.020	0.0053	0.0004	**0.0002**
		0.5	0.024	0.0053	0.0005	**8.53×10^{-6}**
		1	0.023	0.0053	0.0005	**1.51×10^{-5}**
Physical and physiological measures	Blood Pressure: Diastolic	0.01	0.001	0.0052	1.53×10^{-6}	0.8132
		0.05	0.004	0.0052	1.22×10^{-5}	0.5044
		0.1	0.000	0.0053	6.52×10^{-8}	0.9611
		0.5	0.003	0.0053	7.91×10^{-6}	0.5911
		1	0.003	0.0053	9.49×10^{-6}	0.5563
	Blood Pressure: Systolic	0.01	0.008	0.0052	0.0001	0.1138
		0.05	0.008	0.0052	0.0001	0.1324
		0.1	0.013	0.0052	0.0002	**0.0116**
		0.5	0.007	0.0053	0.0001	0.1582
		1	0.008	0.0053	0.0001	0.1211
	BMI	0.01	−0.022	0.0052	0.0005	**2.92×10^{-5}**
		0.05	−0.024	0.0052	0.0006	**3.44×10^{-6}**
		0.1	−0.024	0.0052	0.0006	**6.49×10^{-6}**
		0.5	−0.027	0.0052	0.0007	**3.34×10^{-7}**
		1	−0.026	0.0052	0.0007	**8.52×10^{-7}**

	Height	0.01	0.017	0.0053	0.0003	**0.0011**
		0.05	0.019	0.0053	0.0004	**0.0003**
		0.1	0.019	0.0054	0.0003	**0.0004**
		0.5	0.021	0.0054	0.0004	**0.0001**
		1	0.021	0.0054	0.0004	**0.0001**
	Longevity	0.01	0.004	0.0053	1.87×10^{-5}	0.4091
		0.05	0.000	0.0053	4.62×10^{-8}	0.9673
		0.1	0.000	0.0052	7.30×10^{-8}	0.9588
		0.5	0.000	0.0052	1.31×10^{-7}	0.9449
		1	0.000	0.0052	1.98×10^{-8}	0.9786
	Forced Expiratory Volume in 1s (FEV_1)	0.01	0.000	0.0052	2.08×10^{-7}	0.9306
		0.05	0.007	0.0052	0.0001	0.1604
		0.1	0.007	0.0052	4.38×10^{-5}	0.2064
		0.5	0.012	0.0052	0.0001	0.0220
		1	0.011	0.0052	0.0001	0.0319
Life-course Cognitive Traits and Proxies	Childhood Cognitive Ability	0.01	0.031	0.0052	0.0010	$\mathbf{3.12\times10^{-9}}$
		0.05	0.052	0.0052	0.0027	$\mathbf{2.55\times10^{-23}}$
		0.1	0.063	0.0052	0.0040	$\mathbf{1.45\times10^{-33}}$
		0.5	0.077	0.0052	0.0059	$\mathbf{1.70\times10^{-48}}$
		1	0.079	0.0052	0.0062	$\mathbf{3.49\times10^{-51}}$
	College degree	0.01	0.069	0.0052	0.0048	$\mathbf{3.92\times10^{-40}}$
		0.05	0.085	0.0052	0.0071	$\mathbf{1.05\times10^{-58}}$
		0.1	0.095	0.0052	0.0089	$\mathbf{5.93\times10^{-73}}$
		0.5	0.102	0.0052	0.0102	$\mathbf{3.19\times10^{-83}}$
		1	0.101	0.0052	0.0101	$\mathbf{2.56\times10^{-82}}$
	Years of Education	0.01	0.077	0.0052	0.0058	$\mathbf{1.88\times10^{-48}}$
		0.05	0.090	0.0052	0.0080	$\mathbf{2.26\times10^{-65}}$
		0.1	0.096	0.0052	0.0091	$\mathbf{7.36\times10^{-75}}$
		0.5	0.105	0.0053	0.0109	$\mathbf{6.20\times10^{-89}}$
		1	0.106	0.0053	0.0109	$\mathbf{2.96\times10^{-89}}$

Supplementary Table 4b

Associations between polygenic profiles of health related traits and Reaction Time (log transformed) controlling for age, sex, assessment centre, genotyping batch and array, and ten principal components for population structure. Statistically significant values (P<0.0188) are shown in bold. Cognitive/education phenotypes are scored such that higher scores indicate better performance.

Trait category	Trait	Reaction Time				
		Threshold	β	SE	R2	p
Vascular-Metabolic Diseases	Coronary Artery Disease	0.01	3.24×10^{-5}	0.0005	3.03×10^{-8}	0.9508
		0.05	2.80×10^{-4}	0.0005	2.27×10^{-6}	0.5939
		0.1	0.001	0.0005	2.33×10^{-5}	0.0875
		0.5	0.001	0.0005	1.37×10^{-5}	0.1894
		1	0.001	0.0005	1.83×10^{-5}	0.1301
	Stroke: Ischaemic	0.01	−0.001	0.0005	2.46×10^{-5}	0.0791
		0.05	-3.00×10^{-4}	0.0005	2.53×10^{-6}	0.5735
		0.1	2.52×10^{-4}	0.0005	1.76×10^{-6}	0.6385
		0.5	-3.68×10^{-5}	0.0005	3.73×10^{-8}	0.9455
		1	-1.53×10^{-4}	0.0005	6.58×10^{-7}	0.7740
	Stroke: Cardioembolic	0.01	0.001	0.0005	2.42×10^{-5}	0.0817
		0.05	0.001	0.0005	1.47×10^{-5}	0.1746
		0.1	0.001	0.0005	7.98×10^{-6}	0.3175
		0.5	1.74×10^{-4}	0.0005	8.71×10^{-7}	0.7412
		1	-2.32×10^{-5}	0.0005	1.55×10^{-8}	0.9648
	Stroke: Large Vessel Disease	0.01	5.86×10^{-5}	0.0005	9.86×10^{-8}	0.9115
		0.05	2.26×10^{-4}	0.0005	1.44×10^{-6}	0.6714
		0.1	-1.54×10^{-4}	0.0005	6.66×10^{-7}	0.7726
		0.5	4.45×10^{-6}	0.0005	5.72×10^{-10}	0.9932
		1	-2.03×10^{-4}	0.0005	1.19×10^{-6}	0.6991
	Stroke: Small Vessel Disease	0.01	-3.12×10^{-4}	0.0005	2.82×10^{-6}	0.5525
		0.05	1.05×10^{-4}	0.0005	3.16×10^{-7}	0.8424
		0.1	-1.45×10^{-4}	0.0005	6.04×10^{-7}	0.7832
		0.5	-4.53×10^{-4}	0.0005	5.94×10^{-6}	0.3882
		1	−0.001	0.0005	7.93×10^{-6}	0.3188
	Type 2 Diabetes	0.01	-4.33×10^{-4}	0.0005	5.36×10^{-6}	0.4124
		0.05	-3.10×10^{-4}	0.0005	2.71×10^{-6}	0.5602
		0.1	-4.50×10^{-4}	0.0005	5.70×10^{-6}	0.3982
		0.5	-3.65×10^{-5}	0.0005	3.67×10^{-8}	0.9459
		1	-8.44×10^{-5}	0.0005	1.96×10^{-7}	0.8755
Neuro-Psychiatric Disorders	ADHD	0.01	-2.71×10^{-4}	0.0005	2.13×10^{-6}	0.6053
		0.05	6.76×10^{-5}	0.0005	1.32×10^{-7}	0.8976
		0.1	4.14×10^{-5}	0.0005	4.97×10^{-8}	0.9371
		0.5	−0.001	0.0005	8.45×10^{-6}	0.3036
		1	−0.001	0.0005	1.06×10^{-5}	0.2485
	Alzheimer's Disease	0.01	-4.31×10^{-4}	0.0005	5.38×10^{-6}	0.4116
		0.05	−0.001	0.0005	2.04×10^{-5}	0.1096
		0.1	-2.30×10^{-4}	0.0005	1.53×10^{-6}	0.6619
		0.5	−0.001	0.0005	3.02×10^{-5}	0.0516
		1	−0.001	0.0005	2.64×10^{-5}	0.0692
	Autism	0.01	0.001	0.0005	1.78×10^{-5}	0.1348

		0.05	0.001	0.0005	1.24×10^{-5}	0.2124
		0.1	0.001	0.0005	1.95×10^{-5}	0.1176
		0.5	0.001	0.0005	1.01×10^{-5}	0.2612
		1	0.001	0.0005	1.01×10^{-5}	0.2605
	Bipolar Disorder	0.01	−0.002	0.0005	9.08×10^{-5}	**0.0007**
		0.05	−0.002	0.0005	7.79×10^{-5}	**0.0018**
		0.1	−0.002	0.0005	8.68×10^{-5}	**0.0010**
		0.5	−0.002	0.0005	8.54×10^{-5}	**0.0011**
		1	−0.002	0.0005	8.98×10^{-5}	**0.0008**
	Major Depressive Disorder	0.01	−0.001	0.0005	2.95×10^{-5}	0.0544
		0.05	−0.002	0.0005	7.22×10^{-5}	**0.0026**
		0.1	−0.002	0.0005	9.61×10^{-5}	**0.0005**
		0.5	−0.002	0.0005	8.30×10^{-5}	**0.0013**
		1	−0.002	0.0005	6.50×10^{-5}	**0.0043**
	Schizophrenia	0.01	−0.005	0.0005	0.0007	$\mathbf{4.24\times10^{-22}}$
		0.05	−0.005	0.0005	0.0008	$\mathbf{1.03\times10^{-23}}$
		0.1	−0.006	0.0005	0.0009	$\mathbf{1.88\times10^{-25}}$
		0.5	−0.005	0.0005	0.0008	$\mathbf{7.56\times10^{-24}}$
		1	−0.005	0.0005	0.0008	$\mathbf{2.38\times10^{-23}}$
Brain Measures	Hippocampal Volume	0.01	0.001	0.0005	8.02×10^{-6}	0.3163
		0.05	0.001	0.0005	1.47×10^{-5}	0.1744
		0.1	0.001	0.0005	1.68×10^{-5}	0.1465
		0.5	0.001	0.0005	1.99×10^{-5}	0.1144
		1	0.001	0.0005	1.98×10^{-5}	0.1156
	Intracranial Volume	0.01	0.001	0.0005	7.56×10^{-6}	0.3306
		0.05	3.57×10^{-4}	0.0005	3.60×10−6	0.5020
		0.1	3.32×10^{-4}	0.0005	3.08×10^{-6}	0.5346
		0.5	3.29×10^{-4}	0.0005	2.97×10^{-6}	0.5418
		1	3.21×10^{-4}	0.0005	2.83×10^{-6}	0.5514
	Infant Head Circumference	0.01	−0.001	0.0005	3.16×10^{-5}	0.0468
		0.05	-3.01×10^{-4}	0.0005	2.60×10^{-6}	0.5683
		0.1	-1.06×10^{-4}	0.0005	3.20×10^{-7}	0.8413
		0.5	-1.92×10^{-4}	0.0005	1.05×10^{-6}	0.7174
		1	-2.02×10^{-4}	0.0005	1.15×10^{-6}	0.7037
Physical and physiological measures	Blood Pressure: Diastolic	0.01	0.001	0.0005	1.14×10^{-5}	0.2325
		0.05	1.59×10^{-4}	0.0005	7.28×10^{-7}	0.7627
		0.1	3.45×10^{-4}	0.0005	3.43×10^{-6}	0.5120
		0.5	4.50×10^{-4}	0.0005	5.82×10^{-6}	0.3931
		1	0.001	0.0005	7.61×10^{-6}	0.3289
	Blood Pressure: Systolic	0.01	-1.73×10^{-4}	0.0005	8.68×10^{-7}	0.7416
		0.05	-2.58×10^{-4}	0.0005	1.92×10^{-6}	0.6241
		0.1	-4.81×10^{-4}	0.0005	6.66×10^{-6}	0.3609
		0.5	-4.97×10^{-4}	0.0005	7.09×10^{-6}	0.3460
		1	-3.88×10^{-4}	0.0005	4.32×10^{-6}	0.4619
	BMI	0.01	3.96×10^{-4}	0.0005	4.54×10^{-6}	0.4507
		0.05	1.99×10^{-5}	0.0005	1.15×10^{-8}	0.9697
		0.1	-4.02×10^{-5}	0.0005	4.67×10^{-8}	0.9390
		0.5	-2.47×10^{-5}	0.0005	1.76×10^{-8}	0.9626
		1	1.79×10^{-5}	0.0005	9.25×10^{-9}	0.9728

	Height	0.01	3.64×10^{-4}	0.0005	3.75×10^{-6}	0.4933
		0.05	2.82×10^{-4}	0.0005	2.21×10^{-6}	0.5985
		0.1	4.06×10^{-4}	0.0005	4.54×10^{-6}	0.4508
		0.5	4.46×10^{-4}	0.0005	5.34×10^{-6}	0.4135
		1	4.07×10^{-4}	0.0005	4.43×10^{-6}	0.4562
	Longevity	0.01	2.47×10^{-5}	0.0005	1.75×10^{-8}	0.9627
		0.05	3.23×10^{-4}	0.0005	2.96×10^{-6}	0.5426
		0.1	1.21×10^{-4}	0.0005	4.25×10^{-7}	0.8176
		0.5	2.30×10^{-4}	0.0005	1.52×10^{-6}	0.6623
		1	1.84×10^{-4}	0.0005	9.73×10^{-7}	0.7270
	Forced Expiratory Volume in 1s (FEV_1)	0.01	-4.27×10^{-4}	0.0005	5.28×10^{-6}	0.4162
		0.05	−0.001	0.0005	1.83×10^{-5}	0.1302
		0.1	−0.001	0.0005	1.05×10^{-5}	0.2505
		0.5	-2.14×10^{-4}	0.0005	1.33×10^{-6}	0.6836
		1	-2.52×10^{-4}	0.0005	1.84×10^{-6}	0.6310
Life-course Cognitive Traits and Proxies	Childhood Cognitive Ability	0.01	0.001	0.0005	1.57×10^{-5}	0.1613
		0.05	0.002	0.0005	8.41×10^{-5}	**0.0012**
		0.1	0.002	0.0005	9.30×10^{-5}	**0.0006**
		0.5	0.002	0.0005	0.0001	**0.0002**
		1	0.002	0.0005	8.94×10^{-5}	**0.0008**
	College Degree	0.01	0.001	0.0005	1.60×10^{-5}	0.1573
		0.05	0.001	0.0005	4.61×10^{-5}	**0.0163**
		0.1	0.001	0.0005	3.97×10^{-5}	0.0257
		0.5	0.001	0.0005	4.90×10^{-5}	**0.0133**
		1	0.001	0.0005	4.42×10^{-5}	**0.0186**
	Years of Education	0.01	0.001	0.0005	2.26×10^{-5}	0.0927
		0.05	0.001	0.0005	2.15×10^{-5}	0.1008
		0.1	0.001	0.0005	4.67×10^{-5}	**0.0156**
		0.5	0.001	0.0005	2.71×10^{-5}	0.0654
		1	0.001	0.0005	2.92×10^{-5}	0.0558

Supplementary Table 4c

Associations between polygenic profiles of health related traits, and memory controlling for age, sex, assessment centre, genotyping batch and array, and ten principal components for population structure. Statistically significant values (P<0.0188) are shown in bold. Cognitive/education phenotypes are scored such that higher scores indicate better performance.

Trait category	Trait	Memory				
		Threshold	β	SE	R2	p
Vascular-Metabolic Diseases	Coronary Artery Disease	0.01	−0.003	0.0030	1.20×10^{-5}	0.2399
		0.05	−0.002	0.0030	5.65×10^{-6}	0.4207
		0.1	−0.0003	0.0030	8.02×10^{-8}	0.9236
		0.5	0.0003	0.0030	1.17×10^{-7}	0.9079
		1	0.001	0.0030	3.17×10^{-7}	0.8487
	Stroke: Ischaemic	0.01	−0.002	0.0030	3.97×10^{-6}	0.4995
		0.05	−0.001	0.0030	4.35×10^{-7}	0.8231
		0.1	−0.0005	0.0030	2.23×10^{-7}	0.8728
		0.5	−0.004	0.0030	1.58×10^{-5}	0.1782
		1	−0.003	0.0030	1.12×10^{-5}	0.2562
	Stroke: Cardioembolic	0.01	0.004	0.0030	1.43×10^{-5}	0.2002
		0.05	−0.001	0.0030	9.14×10^{-7}	0.7460
		0.1	−0.004	0.0030	1.39×10^{-5}	0.2071
		0.5	0.004	0.0030	1.52×10^{-5}	0.1870
		1	0.005	0.0030	2.85×10^{-5}	0.0707
	Stroke: Large Vessel Disease	0.01	−0.005	0.0030	2.91×10^{-5}	0.0678
		0.05	−0.006	0.0030	3.15×10^{-5}	0.0573
		0.1	−0.008	0.0030	6.89×10^{-5}	**0.0049**
		0.5	0.0001	0.0030	4.07×10^{-9}	0.9828
		1	−0.001	0.0030	1.55×10^{-6}	0.6727
	Stroke: Small Vessel Disease	0.01	−0.005	0.0030	2.12×10^{-5}	0.1191
		0.05	−0.004	0.0030	1.54×10^{-5}	0.1834
		0.1	−0.003	0.0030	7.26×10^{-6}	0.3612
		0.5	−0.004	0.0030	1.59×10^{-5}	0.1765
		1	−0.003	0.0030	1.19×10^{-5}	0.2431
	Type 2 Diabetes	0.01	0.0002	0.0030	2.52×10^{-8}	0.9572
		0.05	0.002	0.0030	4.55×10^{-6}	0.4697
		0.1	0.001	0.0030	2.81×10^{-7}	0.8575
		0.5	0.003	0.0030	8.32×10^{-6}	0.3285
		1	0.003	0.0030	1.12×10^{-5}	0.2562
Neuro-Psychiatric Disorders	ADHD	0.01	0.0001	0.0030	1.01×10^{-8}	0.9728
		0.05	−0.001	0.0030	4.60×10^{-7}	0.8184
		0.1	0.001	0.0030	7.67×10^{-7}	0.7667
		0.5	0.001	0.0030	1.78×10^{-6}	0.6511
		1	0.001	0.0030	2.61×10^{-7}	0.8627
	Alzheimer's Disease	0.01	−0.009	0.0030	7.37×10^{-5}	**0.0036**
		0.05	−0.009	0.0030	7.37×10^{-5}	**0.0036**
		0.1	−0.011	0.0030	1.26×10^{-4}	**0.0001**
		0.5	−0.010	0.0030	9.05×10^{-5}	**0.0013**
		1	−0.009	0.0030	8.66×10^{-5}	**0.0016**
	Autism	0.01	0.002	0.0030	2.30×10^{-6}	0.6072

		0.05	0.001	0.0030	1.31×10^{-6}	0.6983
		0.1	0.003	0.0030	7.77×10^{-6}	0.3450
		0.5	−0.001	0.0030	1.00×10^{-6}	0.7345
		1	−0.001	0.0030	1.43×10^{-6}	0.6856
	Bipolar Disorder	0.01	−0.013	0.0030	1.56×10^{-4}	**2.27×10^{-5}**
		0.05	−0.015	0.0030	2.12×10^{-4}	**8.12×10^{-7}**
		0.1	−0.015	0.0030	2.30×10^{-4}	**2.70×10^{-7}**
		0.5	−0.017	0.0030	2.74×10^{-4}	**2.02×10^{-8}**
		1	−0.016	0.0030	2.39×10^{-4}	**1.63×10^{-7}**
	Major Depressive Disorder	0.01	−0.007	0.0030	4.88×10^{-5}	**0.0179**
		0.05	−0.006	0.0030	3.68×10^{-5}	0.0398
		0.1	−0.010	0.0030	9.61×10^{-5}	**0.0009**
		0.5	−0.013	0.0030	1.63×10^{-4}	**1.49×10^{-5}**
		1	−0.014	0.0030	1.87×10^{-4}	**3.67×10^{-6}**
	Schizophrenia	0.01	−0.035	0.0030	1.20×10^{-3}	**8.91×10^{-32}**
		0.05	−0.039	0.0030	1.50×10^{-3}	**1.98×10^{-3}9**
		0.1	−0.040	0.0030	1.52×10^{-3}	**9.27×10^{-40}**
		0.5	−0.038	0.0030	1.37×10^{-3}	**3.38×10^{-36}**
		1	−0.038	0.0030	1.32×10^{-3}	**6.33×10^{-35}**
Brain Measures	Hippocampal Volume	0.01	−0.003	0.0030	7.55×10^{-6}	0.3520
		0.05	−0.003	0.0030	1.15×10^{-5}	0.2504
		0.1	−0.005	0.0030	2.65×10^{-5}	0.0812
		0.5	−0.003	0.0030	7.42×10^{-6}	0.3561
		1	−0.003	0.0030	1.04×10^{-5}	0.2756
	Intracranial Volume	0.01	0.0003	0.0030	1.01×10^{-7}	0.9141
		0.05	0.001	0.0030	3.92×10^{-7}	0.8319
		0.1	0.004	0.0030	1.67×10^{-5}	0.1660
		0.5	0.005	0.0030	2.63×10^{-5}	0.0821
		1	0.005	0.0030	2.77×10^{-5}	0.0745
	Infant Head Circumference	0.01	0.002	0.0030	4.06×10^{-6}	0.4947
		0.05	0.001	0.0030	1.45×10^{-6}	0.6830
		0.1	0.005	0.0030	2.78×10^{-5}	0.0742
		0.5	0.003	0.0030	8.28×10^{-6}	0.3297
		1	0.002	0.0030	4.78×10^{-6}	0.4588
Physical and physiological measures	Blood Pressure: Diastolic	0.01	0.002	0.0030	4.34×10^{-6}	0.4803
		0.05	−0.0004	0.0030	1.41×10^{-7}	0.8986
		0.1	0.001	0.0030	1.32×10^{-6}	0.6968
		0.5	−0.001	0.0030	1.68×10^{-6}	0.6607
		1	−0.002	0.0030	2.90×10^{-6}	0.5638
	Blood Pressure: Systolic	0.01	−0.002	0.0030	4.60×10^{-6}	0.4674
		0.05	−0.003	0.0030	7.37×10^{-6}	0.3578
		0.1	−0.002	0.0030	2.34×10^{-6}	0.6039
		0.5	−0.003	0.0030	7.00×10^{-6}	0.3699
		1	−0.002	0.0030	3.99×10^{-6}	0.4985
	BMI	0.01	0.009	0.0030	7.54×10^{-5}	**0.0033**
		0.05	0.013	0.0030	1.68×10^{-4}	**1.16×10^{-5}**
		0.1	0.016	0.0030	2.60×10^{-4}	**4.76×10^{-8}**
		0.5	0.014	0.0030	1.97×10^{-4}	**1.96×10^{-6}**
		1	0.014	0.0030	1.97×10^{-4}	**1.99×10^{-6}**

	Height	0.01	0.003	0.0030	7.70×10^{-6}	0.3472
		0.05	0.001	0.0030	1.76×10^{-6}	0.6534
		0.1	0.002	0.0030	2.41×10^{-6}	0.5991
		0.5	0.001	0.0031	1.90×10^{-6}	0.6407
		1	0.001	0.0031	9.21×10^{-7}	0.7451
	Longevity	0.01	0.004	0.0030	1.66×10^{-5}	0.1680
		0.05	0.003	0.0030	1.13×10^{-5}	0.2539
		0.1	0.004	0.0030	1.73×10^{-5}	0.1583
		0.5	0.005	0.0030	2.24×10^{-5}	0.1087
		1	0.005	0.0030	2.88×10^{-5}	0.0689
	Forced Expiratory Volume in 1s (FEV_1)	0.01	−0.005	0.0030	2.40×10^{-5}	0.0968
		0.05	−0.005	0.0030	2.60×10^{-5}	0.0840
		0.1	−0.005	0.0030	2.04×10^{-5}	0.1256
		0.5	−0.005	0.0030	2.48×10^{-5}	0.0917
		1	−0.005	0.0030	2.66×10^{-5}	0.0806
Life-course Cognitive Traits and Proxies	Childhood Cognitive Ability	0.01	0.003	0.0030	1.21×10^{-5}	0.2395
		0.05	0.006	0.0030	3.23×10^{-5}	0.0543
		0.1	0.007	0.0030	5.49×10^{-5}	**0.0121**
		0.5	0.014	0.0030	1.87×10^{-4}	$\mathbf{3.54\times10^{-6}}$
		1	0.014	0.0030	2.03×10^{-4}	$\mathbf{1.38\times10^{-6}}$
	College degree	0.01	0.0002	0.0030	2.98×10^{-8}	0.9534
		0.05	−0.002	0.0030	5.65×10^{-6}	0.4207
		0.1	−0.002	0.0030	5.32×10^{-6}	0.4344
		0.5	0.001	0.0030	1.32×10^{-6}	0.6970
		1	0.002	0.0030	2.26×10^{-6}	0.6106
	Years of Education	0.01	−0.0005	0.0030	2.11×10^{-7}	0.8765
		0.05	−0.004	0.0030	1.81×10^{-5}	0.1496
		0.1	−0.004	0.0030	1.22×10^{-5}	0.2358
		0.5	−0.002	0.0030	6.11×10^{-6}	0.4022
		1	−0.002	0.0030	2.69×10^{-6}	0.5787

Supplementary Table 4d

Associations between polygenic profiles of health related traits, and college controlling for age, sex, assessment centre, genotyping batch and array, and ten principal components for population structure. Statistically significant values (P<0.0188) are shown in bold. Cognitive/education phenotypes are scored such that higher scores indicate better performance.

Trait category	**Trait**	**Educational Attainment**				
		Threshold	β	SE	R2	p
Vascular-Metabolic Diseases	Coronary Artery Disease	0.01	−0.020	0.0066	0.0001	**0.0020**
		0.05	−0.026	0.0066	0.0002	**0.0001**
		0.1	−0.033	0.0066	0.0003	**8.09×10^{-7}**
		0.5	−0.047	0.0066	0.0006	**8.32×10^{-13}**
		1	−0.047	0.0066	0.0006	**7.92×10^{-13}**
	Stroke: Ischaemic	0.01	−0.013	0.0066	4.64×10^{-5}	0.0539
		0.05	−0.020	0.0067	0.0001	**0.0032**
		0.1	−0.016	0.0067	0.0001	**0.0171**
		0.5	−0.020	0.0068	0.0001	**0.0026**
		1	−0.013	0.0068	4.67×10^{-5}	0.0534
	Stroke: Cardioembolic	0.01	−0.0001	0.0066	6.41×10^{-9}	0.9819
		0.05	−0.001	0.0066	1.43×10^{-7}	0.9148
		0.1	0.001	0.0066	2.76×10^{-7}	0.8817
		0.5	−0.003	0.0066	1.94×10^{-6}	0.6931
		1	0.000	0.0066	$4.94\times10^{-1}2$	0.9995
	Stroke: Large Vessel Disease	0.01	−0.023	0.0066	0.0002	**0.0005**
		0.05	−0.025	0.0067	0.0002	**0.0001**
		0.1	−0.031	0.0067	0.0003	**5.31×10^{-6}**
		0.5	0.008	0.0066	1.70×10^{-5}	0.2438
		1	0.001	0.0066	5.27×10^{-7}	0.8372
	Stroke: Small Vessel Disease	0.01	−0.024	0.0066	0.0002	**0.0003**
		0.05	−0.030	0.0066	0.0003	**5.89×10^{-6}**
		0.1	−0.034	0.0066	0.0003	**2.96×10^{-7}**
		0.5	0.000	0.0066	3.41×10^{-8}	0.9583
		1	0.002	0.0066	1.15×10^{-6}	0.7615
	Type 2 Diabetes	0.01	−0.023	0.0066	0.0001	**0.0006**
		0.05	−0.021	0.0067	0.0001	**0.0020**
		0.1	−0.025	0.0067	0.0002	**0.0002**
		0.5	−0.025	0.0067	0.0002	**0.0002**
		1	−0.024	0.0068	0.0002	**0.0003**
Neuro-Psychiatric Disorders	ADHD	0.01	−0.010	0.0066	2.73×10^{-5}	0.1391
		0.05	−0.016	0.0066	0.0001	**0.0138**
		0.1	−0.022	0.0066	0.0001	**0.0007**
		0.5	−0.025	0.0066	0.0002	**0.0001**
		1	−0.027	0.0066	0.0002	**4.68×10^{-5}**
	Alzheimer's Disease	0.01	−0.013	0.0066	4.51×10^{-5}	0.0572
		0.05	−0.034	0.0066	0.0003	**2.53×10^{-7}**
		0.1	−0.038	0.0066	0.0004	**7.00×10^{-9}**
		0.5	−0.046	0.0066	0.0006	**2.52×10^{-12}**
		1	−0.046	0.0066	0.0006	**2.33×10^{-12}**
	Autism	0.01	0.046	0.0066	0.0006	**4.09×10^{-12}**

		0.05	0.061	0.0066	0.0011	**1.68×10^{-20}**
		0.1	0.060	0.0066	0.0010	**1.42×10^{-19}**
		0.5	0.068	0.0066	0.0013	**5.00×10^{-25}**
		1	0.067	0.0066	0.0013	**2.88×10^{-24}**
	Bipolar Disorder	0.01	0.032	0.0066	0.0003	**9.40×10^{-7}**
		0.05	0.046	0.0066	0.0006	**3.80×10^{-12}**
		0.1	0.050	0.0066	0.0007	**3.41×10^{-14}**
		0.5	0.057	0.0067	0.0009	**1.35×10^{-17}**
		1	0.055	0.0067	0.0008	**2.60×10^{-16}**
	Major Depressive Disorder	0.01	0.004	0.0066	4.03×10^{-6}	0.5700
		0.05	0.003	0.0066	2.61×10^{-6}	0.6475
		0.1	0.003	0.0067	2.22×10^{-6}	0.6731
		0.5	−0.006	0.0067	1.14×10^{-5}	0.3400
		1	−0.009	0.0067	2.14×10^{-5}	0.1905
	Schizophrenia	0.01	0.022	0.0066	0.0001	**0.0008**
		0.05	0.025	0.0067	0.0002	**0.0002**
		0.1	0.024	0.0067	0.0002	**0.0004**
		0.5	0.022	0.0068	0.0001	**0.0012**
		1	0.021	0.0068	0.0001	**0.0017**
Brain Measures	Hippocampal Volume	0.01	−0.007	0.0066	1.27×10^{-5}	0.3132
		0.05	−0.001	0.0066	6.01×10^{-7}	0.8262
		0.1	0.005	0.0066	6.29×10^{-6}	0.4778
		0.5	0.007	0.0066	1.40×10^{-5}	0.2887
		1	0.005	0.0066	8.49×10^{-6}	0.4095
	Intracranial Volume	0.01	0.031	0.0066	2.81×10^{-4}	**2.08×10^{-6}**
		0.05	0.034	0.0067	0.0003	**4.30×10^{-7}**
		0.1	0.039	0.0067	0.0004	**7.92×10^{-9}**
		0.5	0.041	0.0068	0.0005	**8.86×10^{-10}**
		1	0.043	0.0068	0.0005	**2.91×10^{-10}**
	Infant Head Circumference	0.01	0.035	0.0066	0.0003	**1.64×10^{-7}**
		0.05	0.038	0.0066	0.0004	**6.43×10^{-9}**
		0.1	0.050	0.0066	0.0007	**4.01×10^{-14}**
		0.5	0.049	0.0067	0.0007	**1.37×10^{-13}**
		1	0.049	0.0067	0.0007	**2.32×10^{-13}**
Physical and physiological measures	Blood Pressure: Diastolic	0.01	0.004	0.0066	5.75×10^{-6}	0.4971
		0.05	0.020	0.0066	0.0001	**0.0022**
		0.1	0.022	0.0066	0.0001	**0.0011**
		0.5	0.020	0.0066	0.0001	**0.0028**
		1	0.018	0.0066	0.0001	**0.0053**
	Blood Pressure: Systolic	0.01	0.017	0.0066	0.0001	**0.0095**
		0.05	0.032	0.0066	0.0003	**8.25×10^{-7}**
		0.1	0.035	0.0066	0.0004	**7.61×10^{-8}**
		0.5	0.027	0.0066	0.0002	**4.66×10^{-5}**
		1	0.027	0.0066	0.0002	**4.35×10^{-5}**
	BMI	0.01	−0.065	0.0066	0.0012	**3.15×10^{-23}**
		0.05	−0.074	0.0066	0.0016	**2.80×10^{-29}**
		0.1	−0.081	0.0066	0.0019	**7.97×10^{-35}**
		0.5	−0.093	0.0066	0.0025	**6.40×10^{-45}**
		1	−0.093	0.0066	0.0025	**1.07×10^{-44}**

	Height	0.01	0.054	0.0067	0.0008	**8.35×10^{-16}**
		0.05	0.062	0.0067	0.0011	**3.00×10^{-20}**
		0.1	0.066	0.0068	0.0012	**9.82×10^{-23}**
		0.5	0.069	0.0069	0.0013	**4.84×10^{-24}**
		1	0.070	0.0069	0.0013	**2.95×10^{-24}**
	Longevity	0.01	NA	NA	NA	NA
		0.05	NA	NA	NA	NA
		0.1	NA	NA	NA	NA
		0.5	NA	NA	NA	NA
		1	NA	NA	NA	NA
	Forced Expiratory Volume in 1s (FEV_1)	0.01	NA	NA	NA	NA
		0.05	NA	NA	NA	NA
		0.1	NA	NA	NA	NA
		0.5	NA	NA	NA	NA
		1	NA	NA	NA	NA
Life-course Cognitive Traits and Proxies	Childhood Cognitive Ability	0.01	0.062	0.0066	0.0011	**$5.29\times10^{-2}1$**
		0.05	0.095	0.0066	0.0026	**1.67×10^{-46}**
		0.1	0.106	0.0066	0.0032	**4.17×10^{-58}**
		0.5	0.120	0.0066	0.0041	**9.28×10^{-74}**
		1	0.122	0.0066	0.0042	**3.92×10^{-75}**
	College degree	0.01	0.205	0.0067	0.0118	**1.47×10^{-206}**
		0.05	0.251	0.0067	0.0175	**1.60×10^{-303}**
		0.1	0.265	0.0068	0.0194	**0**
		0.5	0.280	0.0068	0.0216	**0**
		1	0.279	0.0068	0.0214	**0**
	Years of Education	0.01	0.210	0.0067	0.0124	**1.56×10^{-216}**
		0.05	0.244	0.0067	0.0167	**5.61×10^{-289}**
		0.1	0.265	0.0068	0.0195	**0**
		0.5	0.283	0.0068	0.0220	**0**
		1	0.285	0.0068	0.0223	**0**

Supplementary Table 5

Multivariate models predicting cognitive (and educational) phenotypes, including all polygenic profile scores together with covariates (age, sex, assessment centre, genotyping batch and array, and ten genetic principal components for population structure; covariate values not shown here). All phenotypes scored such that higher scores indicate better performance. Adjusted R^2 values refer to the polygenic profile scores only (excluding variance explained by the covariates). Statistically significant p-values (after False Discovery Rate correction across 94 tests; threshold: p <0.025) shown in bold.

Trait Category	Trait	Verbal-numerical Reasoning (Adj. R^2 = 0.0226)		Memory (Adj. R^2 = 0.0017)		Reaction Time (Adj. R^2 = 0.0012)		Educational Attainment (Adj. R^2 = 0.0333)	
		β	p	β	p	β	p	β	p
Vascular-metabolic Diseases	Coronary Artery Disease	**−0.012**	**0.021**	−0.002	0.506	0.006	0.032	**−0.034**	**<0.001**
	Stroke: Ischaemic	−0.009	0.102	−0.002	0.631	−0.006	0.034	0.002	0.750
	Stroke: Cardioembolic	−0.006	0.204	0.004	0.205	0.005	0.092	0.001	0.884
	Stroke: Large Vessel Disease	−0.008	0.141	**−0.010**	**0.002**	0.002	0.410	**−0.022**	**0.002**
	Stroke: Small Vessel Disease	−0.008	0.113	−0.005	0.097	−0.003	0.338	**−0.028**	**<0.001**
	Type 2 Diabetes	0.004	0.499	0.002	0.510	−0.002	0.450	−0.005	0.484
Neuro-psychiatric Disorders	ADHD	−0.007	0.170	−0.003	0.253	−0.004	0.194	**−0.018**	**0.007**
	Alzheimer's Disease	**−0.018**	**<0.001**	**−0.008**	**0.007**	−0.005	0.089	**−0.034**	**<0.001**
	Autism	**0.018**	**<0.001**	0.004	0.224	0.004	0.147	**0.060**	**<0.001**
	Bipolar Disorder	0.006	0.232	−0.006	0.068	−0.003	0.222	**0.045**	**<0.001**
	Major Depressive Disorder	−0.010	0.061	−0.006	0.053	−0.006	0.025	−0.010	0.147
	Schizophrenia	**−0.061**	**<0.001**	**−0.029**	**<0.001**	**−0.028**	**<0.001**	**0.016**	**0.022**
Brain Measures	Hippocampal Volume	0.005	0.289	−0.004	0.126	0.004	0.121	0.009	0.168
	Intracranial Volume	0.009	0.080	0.005	0.103	0.003	0.282	**0.025**	**<0.001**
	Infant Head Circumference	**0.015**	**0.004**	0.001	0.653	**−0.010**	**<0.001**	**0.041**	**<0.001**
Physical and Physiological Measures	BMI	**−0.014**	**0.007**	**0.015**	**<0.001**	0.003	0.311	**−0.058**	**<0.001**
	Diastolic Blood Pressure	−0.007	0.273	0.004	0.278	0.001	0.635	0.001	0.940
	Height	0.004	0.484	−0.001	0.681	0.001	0.830	**0.037**	**<0.001**
	Longevity	0.003	0.526	0.005	0.068	0.002	0.491	-	-
	Forced Expiratory Volume in 1s	0.009	0.076	−0.004	0.143	−0.003	0.222	-	-
	Systolic Blood Pressure	0.004	0.538	0.0001	0.974	−0.005	0.212	0.015	0.082
Life-course Cognitive Traits and Proxies	Childhood Cognitive Ability	**0.063**	**<0.001**	**0.011**	**<0.001**	**0.008**	**0.004**	**0.095**	**<0.001**
	College Degree	**0.046**	**<0.001**	0.004	0.285	0.005	0.193	**0.140**	**<0.001**
	Years of Education	**0.064**	**<0.001**	−0.003	0.360	0.005	0.187	**0.162**	**<0.001**