Assessing the genetic overlap between BMI and cognitive function

Riccardo E Marioni, PhD[1,2,3,*], **Jian Yang, PhD**[3], **Dominika Dykiert, PhD**[1,4], **René Mõttus, PhD**[1,4], **Archie Campbell, MA**[5], **CHARGE Cognitive Working Group**, **Gail Davies, PhD**[1,4], **Caroline Hayward, PhD**[5,6], **David J Porteous, PhD**[1,2,5], **Peter M Visscher, PhD**[3,7], and **Ian J Deary, PhD**[1,4,5]

[1]Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, 7 George Square, Edinburgh, EH8 9JZ, UK

[2]Medical Genetics Section, Centre for Genomic and Experimental Medicine, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, EH4 2XU, UK

[3]Queensland Brain Institute, The University of Queensland, Brisbane, 4072, QLD, Australia

[4]Department of Psychology, University of Edinburgh, Edinburgh, EH8 9JZ, UK

[5]Generation Scotland, Centre for Genomic and Experimental Medicine, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, EH4 2XU, UK

[6]Medical Research Council Human Genetics Unit, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh EH4 2XU, UK

[7]University of Queensland Diamantina Institute, Translational Research Institute, The University of Queensland, Brisbane 4072, QLD, Australia

Abstract

Obesity and low cognitive function are associated with multiple adverse health outcomes across the life-course. They have a small phenotypic correlation (r=−0.11; high BMI - low cognitive function), but whether they have a shared genetic aetiology is unknown. We investigated the phenotypic and genetic correlations between the traits using data from 6 815 unrelated, genotyped members of Generation Scotland - an ethnically homogeneous cohort from five sites across Scotland. Genetic correlations were estimated using: same-sample bivariate GCTA-GREML; independent samples bivariate GCTA-GREML utilising Generation Scotland for cognitive data, and four other samples (n=20 806) for BMI; and bivariate LDSC analysis utilising the largest GWAS summary data on cognitive function (n=48 462) and BMI (n=339 224) to date. The GWAS summary data were also used to create polygenic scores for the two traits, with within- and cross-

trait prediction taking place in the independent Generation Scotland cohort. A large genetic correlation of −0.51 (SE 0.15) was observed using the same-sample GCTA-GREML approach compared to −0.10 (SE 0.08) from the independent samples GCTA-GREML approach, and −0.22 (SE 0.03) from the bivariate LDSC analysis. A genetic profile score using cognition-specific genetic variants accounts for 0.08% (P=0.020) of the variance in BMI, and a genetic profile score using BMI-specific variants accounts for 0.42% (P=1.9 × 10^{-7}) of the variance in cognitive function. Seven common genetic variants are significantly associated with both traits at P<5 × 10^{-5}, which is significantly more than expected by chance (P=0.007). All these results suggest there are shared genetic contributions to BMI and cognitive function.

Keywords

BMI; cognitive function; genetics; polygenic score

Introduction

The obesity epidemic in the UK is a major public health problem. High body mass index (BMI), a marker of obesity, has been associated with an increased risk of multiple disease and health outcomes, such as type 2 diabetes and cardiovascular disease.[1-3] It has also been associated with lower cognitive function.[4] Possible mechanisms of this link include brain atrophy[5] and type 2 diabetes,[6] although the causality of such associations is not yet clear.[7] Moreover, a recent study identified an association between increased BMI and a lower risk of dementia.[8] Studies show genetic influences on both cognitive function[9] and BMI.[10] Twin models indicate inconsistent findings regarding the genetic correlation between the traits.[11-13] Some report a genetic correlation of around 0.27 (such that genes for poorer cognitive performance correlate associate with genes for a higher BMI),[12] others a genetic correlation of 0.12[13], while one found a null association.[11] However, a genetic correlation has not yet been examined at the molecular genetic level. Identification of any shared genetic contributions could aid our understanding of the phenotypic association between lower cognitive function and higher BMI. This could also shed light on the aetiology of the health outcomes with which both are associated, such as increased mortality risk.[14-17]

Molecular genetic studies have shown that common genetic variants explain around 30% of individual differences in cognitive function[9] and around 10-20% of individual differences in BMI in adults (~30% in adolescents).[18-20] However, this approach, using genome-wide complex trait analysis (GCTA-GREML), does not identify the specific variants and genes that contribute to the associations. One approach that utilises information from specific genetic variants is polygenic scoring, which uses effect sizes (or, the strength of associations of different loci with the phenotype in question) from large GWASs to build linear predictors of the phenotype in independent cohorts. For example, previous studies have shown that a polygenic score for cognitive function (based on a GWAS of 48 462 people) predicts 1.27% of the variance in cognitive function in an independent cohort.[9] One can also examine polygenic scores for correlated traits e.g., a higher polygenic score for schizophrenia is correlated with greater life-course cognitive decline.[21]

Here, we examine the genotypic correlations between cognitive function and BMI. The genetic correlations are calculated using three different approaches: (1) bivariate GCTA-GREML[22,23] where both BMI and cognitive function are measured in the same sample, (2) bivariate GCTA-GREML where the traits are measured in different samples, and (3) LDSC regression[24], which utilises summary GWAS data with potentially overlapping participants for each trait. We also relate polygenic risk scores for the two traits - predicting both within and across traits. Finally, we examine the overlap between existing GWAS analyses of both BMI and cognitive function to identify individual SNP variants and genes that may be involved in shared biological pathways.

Material and Methods

Data for the same-sample GCTA-GREML analysis, the phenotypic correlation analysis, and the independent cohort for the polygenic prediction analysis came from Generation Scotland: the Scottish Family Health Study, a population-based, family-structured cohort that sampled over 24 000 people in Scotland between the years 2006 and 2011.[25,26] The study was set up for family-based genetic epidemiology research; health outcomes including coronary heart disease, stroke, cancer, chronic obstructive pulmonary disease, diabetes, and mental illness are highly prevalent in Scotland. The sampling frame of the study focused on 7 953 probands between ages 35-65 years, who were registered with participating general medical practitioners from five regional centres: Glasgow, Tayside, Ayrshire, Arran, and the North-East of Scotland. The probands were invited to participate through the patient lists at the participating general medical practices; in the UK ~96% of the population is registered with a general practitioner.[26] Up to three generations of the probands' relatives were then recruited. There was no ascertainment bias towards a particular disease or health condition. A full description of the cohort has been given previously[25,26] and at www.generationscotland.org.

Cognitive function data for the independent-samples bivariate GCTA genetic correlation analysis came from Generation Scotland.[25,26] Open access data from dbGaP for the Gene Environment Association Studies initiative (GENEVA) project (comprising three studies, total n=14 347: Atherosclerosis Risk in the Community - ARIC, Nurses' Health Study - NHS, and the Health Professionals' Follow-up Study - HPFS) and the Health and Retirement Study (HRS, n=8,652) were used for the BMI analysis. Their dbGaP accession numbers are phs000090.v1.p1 (ARIC), phs000091.v2.p1 (GENEVA-T2D), and phs000428.v1.p1 (HRS). A summary description of the three cohorts and details about quality controls of genotyped data and imputation can be found elsewhere.[27]

For the LDSC genetic correlation analysis, summary data from the largest GWAS studies to date for cognitive function[9] and BMI[10] were used.

Generation Scotland Ethical details

All components of Generation Scotland received ethical approval from the NHS Tayside Committee on Medical Research Ethics (REC Reference Number: 05/S1401/89). GS:SFHS has also been granted Research Tissue Bank status by the Tayside Committee on Medical

Research Ethics (REC Reference Number: 10/S1402/20), providing generic ethical approval for a wide range of uses within medical research.

Body Mass Index in Generation Scotland

BMI was measured as weight in kilograms divided by height in metres squared (measurement details in Supplementary Information File 1). Participants with a BMI less than 17 or greater than 50 were considered as outliers and removed prior to the analyses.

Cognitive function in Generation Scotland

A general cognitive factor was obtained via a principal components analysis of four cognitive tests that measured processing speed (Wechsler Digit Symbol Substitution Task[28]), verbal declarative memory (Wechsler Logical Memory Test; sum of immediate and delayed recall of one paragraph[29]), executive function (phonemic Verbal Fluency Test; using the letters C, F, and L, each for one minute[30]), and vocabulary (the Mill Hill Vocabulary Scale; junior and senior synonyms combined[31]). The first unrotated principal component, which explained 42% of the variance of the four tests, was extracted and used as the cognitive variable of interest. Three of the four cognitive tests that were used to derive the general cognitive factor were based on verbal stimuli (Verbal Fluency Test, Mill Hill Vocabulary Scale, and the Logical Memory Test); however they, along with the Digit Symbol test, targeted different domains of cognitive function - executive function, vocabulary, memory, and processing speed, respectively. The statistically derived general cognitive factor therefore includes common variance from these four different facets of cognitive function.

Generation Scotland Genotyping

Genome-wide genotyping data were measured on a sub-sample of 10 000 participants using the Illumina HumanOmniExpressExome-8 v1.0 DNA Analysis BeadChip and Infinium chemistry.[32] Measurement details and quality control steps are reported in Supplementary Information File 1. Post-QC, there was an analysis sample of 6 815 unrelated individuals. SNPs with a MAF below 1% were excluded prior to the analysis to prevent rare variants having an influence on the downstream analyses.

Generation Scotland, GENEVA, and HRS imputation and Quality Control

Genotype data in Generation Scotland, GENEVA, and the Health and Retirement Study were imputed to either HapMap2 or 1000G. Imputation details and quality control steps are reported in Supplementary Information File 1. Post-QC, there were 20 806 unrelated individuals for analysis in the combined data set. Both phenotypes were adjusted for age in each gender group in each cohort separately. Since the genotype data were imputed based on different reference panels, we included in the analysis only the SNPs in common with the HapMap3 panel because the HapMap3 SNP set was optimized to capture common genetic variation in the human genome.[33]

Statistical Analyses

All phenotypic data analyses were conducted on the unrelated Generation Scotland cohort who had genome-wide genotyping data available (n=6 815). To determine the associations

between cognitive function and BMI, a linear model was used with general cognitive factor as the independent variable. Age and sex were included as covariates.

Age-, sex-, and population stratification-adjusted residuals for general cognitive function and BMI were computed by linear regression. A conservative number (fourteen) of ancestry components were included.[34] The residual values were carried forward to genome-wide complex trait analyses – GCTA-GREML[22,35] – to obtain the proportion of variation in the variables explained by common single nucleotide polymorphisms. The univariate GCTA-GREML estimates for general cognitive function have been reported previously.[34]

Three methods were used to estimate the genetic correlation between BMI and general cognitive function. First, bivariate GCTA-GREML[23] was run in Generation Scotland where the phenotypic and genotypic information came from the same unrelated individuals. This approach estimates the extent to which genetic similarities correlate with phenotypic similarities. However, the relatively small sample size (and corresponding large standard errors) for this analysis resulted in an imprecise estimate. Second, bivariate GCTA-GREML analysis[23] was used on cognitive data from Generation Scotland and BMI data in American adults from four publicly available datasets. This approach estimates the genetic correlation through the SNP/phenotypic similarities in the independent samples. Third, summary GWAS output from the Davies et al.[9] and Locke et al.[10] papers were used to estimate the genetic correlation via the LDSC regression method[24]. This method does not require raw genotype or phenotype information, nor does it matter if there is an overlap of individuals in the two GWAS analyses. Briefly, this approach utilises LD structure (SNPs in regions of high LD will tag a greater part of the genome than those in low LD) whereby a SNP's association with a phenotype will result from its individual contribution and that of the surrounding SNPs in LD with it. In a bivariate setting, the expectation of the product of the statistical scores (z-scores) for the SNP-phenotype associations can be expressed as an intercept term and another term, including the genetic covariance between the traits, which does not depend on sample overlap for the input GWAS data.

A polygenic score for general cognitive function was calculated using data from a GWAS of general cognitive function (n=48 462)[9]; Generation Scotland did not contribute to the meta-GWAS. The greatest proportion of variance (1.27%, P=1.5×10^{-17}) explained in general cognitive function was for a predictor that utilised SNPs with a P-value less than 0.5 in creating the score.[9] Here, we use the same predictor. For a brief summary of polygenic risk scoring, please see Supplementary Information File 2.

A polygenic score for BMI was created using summary data from a recent meta-analysis, which included 339 224 individuals in a meta-analysis.[10] Generation Scotland was not included in the study. The greatest proportion of phenotypic variance in BMI is explained by a predictor that contains a subset of all HapMap 3 SNPs.[10] We applied this predictor to our data.

Linear regression models were used to assess the relationship between the phenotypes and the polygenic scores, controlling for age, sex, and population stratification (the first 14 PCs).

The polygenic scores were pre-adjusted for age, sex, and the 14 PCs with the residuals being used in the main models.

Using the results from the polygenic prediction analysis, we can provide estimates for the genetic correlation between cognitive function and BMI, based on their theoretical relationships (Supplementary Information File 3).

The GWAS output from the general cognitive function and BMI studies were merged to identify SNPs common to both analyses (Supplementary Information File 4). Significant hits at a suggestive threshold of $P<5 \times 10^{-5}$ in both studies were carried forward as potential polygenic variants that are important for individual differences in both traits. The total number of hits observed was compared to the expected number, based on an assumption of the two traits being independent.

Analyses were carried out in R.[36] The polygenic risk scores were created using Plink.[37,38]

Results

A summary of the Generation Scotland cohort is presented in Table 1. The cohort had a median (IQR) age of 57 (49-63) years. 59% of the cohort was female and the median education attained was 12-13 years. The mean BMI of the cohort was in the overweight range: 27.1 (SD 4.9) kg/m^2. The summary data (means and standard deviations) for the four cognitive tests that were used in the construction of the general cognitive factor are also presented in Table 1.

The age- and sex-adjusted linear regression model (Table 2) yielded a standardised effect size (beta) of −0.10 (SE 0.01, P=1.3 × 10^{-14}, n=6 273) between the phenotypic measures of general cognitive function and BMI - better cognitive function is correlated with lower BMI. There was no evidence for a non-linear association between cognitive function and BMI after controlling for age and sex (P = 0.090). A boxplot showing the distribution of cognitive function scores by BMI decile is presented in Supplementary Information File 5.

Estimates of the SNP-based heritabilities are presented in Table 3. The first approach, utilising data from the Generation Scotland sample alone, found univariate estimates, which represent the proportion of variance in the traits explained by common genetic variants, of 29% (SE 6%) for cognitive function and 28% (SE 6%) for BMI. The estimates for the second approach, which used data from Generation Scotland for cognitive function and the four US-based cohorts for BMI, were 31% (SE 5%) for cognitive function and 22% (SE 2%) for BMI. The estimates for the third approach (LD scoring), which used summary GWAS data from the Davies et al.[9] and Locke et al.[10] papers, were substantially lower for both traits: 15% (SE 1%) for cognitive function and 14% (SE 1%) for BMI.

Estimates of the genetic correlation between cognitive function and BMI for the three approaches are also reported in Table 3. The first method, bivariate GCTA-GREML using data from Generation Scotland for both traits, yielded a genetic correlation of −0.51 (SE 0.15). The estimate of the same genetic correlation was −0.10 (SE 0.08) using the independent-samples GCTA-GREML (GS data for cognitive function, GENEVA and Health

and Retirement Study data for BMI). The estimate for the third approach (LDSC regression), which used the summary GWAS data from Davies et al.[9] and Locke et al.[10] was −0.22 (SE 0.03). All three estimates consistently indicate that the genes associated with better cognitive function are also associated with a lower BMI.

The polygenic predictions, which were built using the GWAS summary data from the Davies et al.[9] and Locke et al.[10] GWASs and applied to the Generation Scotland cohort, are shown in Table 4. The polygenic score for general cognitive function predicted general cognitive function, explaining 0.81% of its variance (P=3.3 × 10^{-13}, n=6 273). The polygenic score for general cognitive function also predicted 0.08% of the variance in BMI (P=0.020, n=6 463). The polygenic predictor for BMI explained 7.1% of the variance in BMI (P<2 × 10^{-16}, n=6 463), consistent with that reported previously,[10] and 0.42% of the variance in general cognitive function (P=1.9 × 10^{-7}, n=6 273).

An analysis of the overlapping SNP variants from the cognition and BMI meta-GWASs identified seven variants (from fours genes: *AKAP6*, *TOMM40*, *TMEM161B*, and *TNRC6B*) that were significant for both traits at P<5 × 10^{-5}, which was greater than by chance (P=0.007) (Supplementary Information File 4).

Discussion

This study found an overlap of genetic influences on two important correlates of health outcomes over the life course: BMI and cognitive function. The phenotypic correlation between the traits was −0.11, indicating that better cognitive function is associated with lower BMI. The three estimates of the genetic correlation ranged between −0.10 and −0.51. A genetic correlation quantifies how genetic variants in one trait are correlated with genetic variants for another trait, averaged over the genome. Here, the gene variants associated with increased cognitive function scores were associated with lower BMI. We also showed, using polygenic risk score predictors derived from independent studies, that individual common genetic variants associated with BMI explain a significant proportion of the variance in cognitive function, and vice versa. These proportions (0.42% and 0.08%) are very small. However, when they are compared to the proportions of variance that each polygenic risk score explained in their own respective phenotype (0.81% and 7.1%), this makes the former appear more substantial. There are seven individual genetic variants (four independent) that are associated with both traits at P<5×10^{-5}, which is significantly more than expected by chance (P=0.007). Taken together, these findings point toward some shared biological underpinnings for BMI and general cognitive function.

The three empirical approaches taken to calculate the genetic correlation along with the theoretically-derived estimate, based on the polygenic prediction results, is a strength of the study. Another strength is the novelty of the hypotheses being tested - using polygenic scores from BMI to predict general cognitive function and vice versa. Such analyses are important as they aid our understanding of common sets of genetic variants that associate with multiple outcomes. We explored this further by examining the overlap of top hits from previous GWAS analyses of general cognitive function and BMI.

Although the Generation Scotland study had a large sample size, the same sample genetic correlation still carried a relatively large standard error. Compared to the same-sample analysis, the independent-samples bivariate GCTA-GREML reduced the SE of the genetic correlation from 0.15 to 0.08, which then dropped further to 0.03 when we utilised the LDSC regression approach. With the decreasing standard error came a convergence of the genetic correlation to an estimate of −0.22 from the LDSC regression analysis, which was contained in the 95% confidence intervals for independent-sample and just inside of the same-sample GCTA-GREML interval. Again, it is worth noting that the same-sample GCTA-GREML estimate was measured with a lack of precision - its 95% confidence interval was [−0.80, −0.22]. Theoretically, we would expect, given the polygenic prediction results, to have observed a genetic correlation of around −0.32 to −0.24 (Supplementary Information File 3), which is in line with the genetic correlation estimated from the LDSC regression analysis. One limitation of the Generation Scotland cohort for this study is the cross sectional nature of the data. It may be the case that the association between BMI and cognitive function is diluted when looking in a cohort with a broad age-range.

The univariate GCTA-GREML estimates obtained here are in accordance with those previously reported for general cognitive function[9] and slightly higher for BMI.[18,19] The small within-trait polygenic prediction estimates correspond to those reported in the literature for cognitive abilities (~1%).[9] The results accord with one of the predictions of the system integrity hypothesis, whereby cognitive function is hypothesised to be associated with health outcomes because they all reflect a common general build quality of an organism.[39-41] These results are also consistent with the finding that BMI-related diabetes is equally strongly associated with lower cognitive function before and after the onset of the disease.[7] Larger meta-analysis GWAS studies for cognitive function and BMI will improve the predictive power of the polygenic predictors. Sequencing studies in very large samples that incorporate rare variants might also help us explain some of the missing heritability between molecular estimates of heritability and twin-based findings.

BMI and cognitive function are associated with numerous health outcomes.[1-3,15,42,43] Whereas the phenotypic correlation between the two traits is small, the genetic correlation is moderate, suggesting common biological pathways. Another possible explanation is that the associations reflect causal pathways. Techniques such as Mendelian Randomisation may help to tease apart the extent to which the pathways are shared versus linear (e.g., genes to cognitive function to BMI).[44] The GWAS hits that are significant for both traits are found in genes linked to insulin-related processes (*AKAP6*), lipid transportation and Alzheimer's disease (*TOMM40*), retinal arteriolar calibre (*TMEM161B*), and height (*TNRC6B*). The *TOMM40* SNP also tags the e4 allele defining SNP of *APOE*. Given the links between type 2 diabetes and impaired cognitive function, retinal microvascular disease and cognitive function, and height with cognitive function (and, obviously BMI) these are plausible candidates that warrant further exploration. It is possible that there is an overlap in the anatomical substrate in the brain for the expression of the genes associated with both cognitive function and BMI.[10] Future studies could consider downstream analyses to investigate if these markers lie on causal pathways for the determination for either trait. For example, epigenetic marks such as DNA methylation have been identified as correlates of

BMI in both blood and adipose tissue[45] as well as correlates of dementia in a case-control study of diabetics.[46]

Understanding the genetics of BMI and its overlap with the genetics of other correlates/predictors of health outcomes e.g., cognitive function, will help elucidate common pathways of disease outcomes. This study identified a small phenotypic correlation between BMI and cognitive function that is roughly half the size of the genetic correlation. Although genetic prediction of these traits is very small when applied to an individual, when coupled with the overlapping SNP hits for the traits, they highlight shared genetic pathways for two important predictors of health outcomes, BMI and cognitive function.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

References

1. Abdullah A, Peeters A, de Courten M, Stoelwinder J. The magnitude of association between overweight and obesity and the risk of diabetes: a meta-analysis of prospective cohort studies. Diabetes Res. Clin. Pract. 2010; 89(3):309–319. [PubMed: 20493574]

2. Poirier P, Giles TD, Bray GA, Hong Y, Stern JS, Pi-Sunyer FX, et al. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. Circulation. 2006; 113(6):898–918. [PubMed: 16380542]

3. Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. J. Am. Coll. Cardiol. 2009; 53(21):1925–1932. [PubMed: 19460605]

4. Sabia S, Kivimaki M, Shipley MJ, Marmot MG, Singh-Manoux A. Body mass index over the adult life course and cognition in late midlife: the Whitehall II Cohort Study. Am. J. Clin. Nutr. 2009; 89(2):601–607. [PubMed: 19073790]

5. Ward MA, Carlsson CM, Trivedi MA, Sager MA, Johnson SC. The effect of body mass index on global brain volume in middle-aged adults: a cross sectional study. BMC Neurol. 2005; 5:23. [PubMed: 16321166]

6. Strachan MW, Reynolds RM, Marioni RE, Price JF. Cognitive function, dementia and type 2 diabetes mellitus in the elderly. Nat. Rev. Endocrinol. 2011; 7(2):108–114. [PubMed: 21263438]

7. Mõttus R, Luciano M, Starr JM, Deary IJ. Diabetes and life-long cognitive ability. J. Psychosom. Res. 2013; 75(3):275–278. [PubMed: 23972418]

8. Qizilbash N, Gregson J, Johnson ME, Pearce N, Douglas I, Wing K, et al. BMI and risk of dementia in two million people over two decades: a retrospective cohort study. Lancet Diabetes Endocrinol. 2015 Epub ahead of print.

9. Davies G, Armstrong N, Bis JC, Bressler J, Chouraki V, Giddaluru S, et al. Genetic contributions to variation in general cognitive function: a meta-analysis of genome-wide association studies in the CHARGE consortium (N=53 949). Mol. Psychiatry. 2015 Epub ahead of print.

10. Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, Day FR, et al. Genetic studies of body mass index yield new insights for obesity biology. Nature. 2015; 518(7538):197–206. [PubMed: 25673413]

11. Benyamin B, Wilson V, Whalley LJ, Visscher PM, Deary IJ. Large, consistent estimates of the heritability of cognitive ability in two entire populations of 11-year-old twins from Scottish mental surveys of 1932 and 1947. Behav. Genet. 2005; 35(5):525–34. [PubMed: 16184482]

12. Frazier-Wood AC, Carnell S, Pena O, Hughes SO, O'Connor TM, Asherson P, Kuntsi J. Cognitive performance and BMI in childhood: Shared genetic influences between reaction time but not response inhibition. Obesity (Silver Spring). 2014; 22(11):2312–8. [PubMed: 25376398]

13. Laitala VS, Kaprio J, Koskenvuo M, Räihä I, Rinne JO, Silventoinen K. Association and causal relationship of midlife obesity and related metabolic disorders with old age cognition. Curr Alzheimer Res. 2011; 8(6):699–706. [PubMed: 21619517]

14. Hart CL, Taylor MD, Davey Smith G, Whalley LJ, Starr JM, Hole DJ, et al. Childhood IQ, social class, deprivation, and their relationships with mortality and morbidity risk in later life: prospective observational study linking the Scottish Mental Survey 1932 and the Midspan studies. Psychosom Med. 2003; 65(5):877–883. [PubMed: 14508035]

15. Osler M, Andersen AM, Due P, Lund R, Damsgaard MT, Holstein BE. Socioeconomic position in early life, birth weight, childhood cognitive function, and adult mortality. A longitudinal study of Danish men born in 1953. J Epidemiol Community Health. 2003; 57(9):681–686. [PubMed: 12933773]

16. Whalley LJ, Deary IJ. Longitudinal cohort study of childhood IQ and survival up to age 76. BMJ. 2001; 322(7290):819. [PubMed: 11290633]

17. Kuh D, Richards M, Hardy R, Butterworth S, Wadsworth ME. Childhood cognitive ability and deaths up until middle age: a post-war birth cohort study. Int. J. Epidemiol. 2004; 33(2):408–413. [PubMed: 15082649]

18. Yang J, Manolio TA, Pasquale LR, Boerwinkle E, Caporaso N, Cunningham JM, et al. Genome partitioning of genetic variation for complex traits using common SNPs. Nat. Genet. 2011; 43:519–525. [PubMed: 21552263]

19. Vattikuti S, Guo J, Chow CC. Heritability and genetic correlations explained by common SNPs for metabolic syndrome traits. PLoS Genet. 2012; 8:e1002637. [PubMed: 22479213]

20. Llewellyn CH, Trzaskowski M, Plomin R, Wardle J. Finding the missing heritability in pediatric obesity: the contribution of genome-wide complex trait analysis. Int. J. Obes. (Lond). 2013; 37(11):1506–1509. [PubMed: 23528754]

21. McIntosh AM, Gow A, Luciano M, Davies G, Liewald DC, Harris SE, et al. Polygenic risk for schizophrenia is associated with cognitive change between childhood and old age. Biol. Psychiatry. 2013; 73(10):938–943. [PubMed: 23419543]

22. Yang J, Lee SH, Goddard ME, Visscher PM. GCTA: a tool for genome-wide complex trait analysis. Am. J. Hum. Genet. 2011; 88(1):76–82. [PubMed: 21167468]

23. Lee SH, Yang J, Goddard ME, Visscher PM, Wray NR. Estimation of pleiotropy between complex diseases using single-nucleotide polymorphism-derived genomic relationships and restricted maximum likelihood. Bioinformatics. 2012; 28(19):2540–2542. [PubMed: 22843982]

24. Bulik-Sullivan BK, Loh PR, Finucane HK, Ripke S, Yang J, Patterson N, et al. LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. Nat. Genet. 2015; 47(3):291–295. [PubMed: 25642630]

25. Smith BH, Campbell H, Blackwood D, Connell J, Connor M, Deary IJ, et al. Generation Scotland: the Scottish Family Health Study; a new resource for researching genes and heritability. BMC Med. Genet. 2006; 7:74. [PubMed: 17014726]

26. Smith BH, Campbell A, Linksted P, Fitzpatrick B, Jackson C, Kerr SM, et al. Cohort profile: Generation Scotland: Scottish Family Health Study (GS:SFHS). The study, its participants and their potential for genetic research on health and illness. Int. J. Epidemiol. 2012; 42(3):689–700. [PubMed: 22786799]

27. Yang J, Bakshi A, Zhu Z, Hemani G, Vinkhuyzen AA, Lee SH, et al. Genetic variance estimation with imputed variants finds negligible missing heritability for human height and body mass index. Nat. Genet. 2015; 47(10):1114–20. [PubMed: 26323059]

28. Wechsler, D. WAIS-III UK Wechsler Adult Intelligence Scale. Psychological Corporation; London, UK: 1998.

29. Wechsler, D. WMS-III UK, Wechsler Memory Scale-Revised. Psychological Corporation; London, UK: 1998.

30. Lezak , MD. Neuropsychological Assessment. 3. Oxford University Press; Oxford, UK: 1995.

31. Raven, JC.; Court, JH.; Raven, J. Manual for Raven's Progressive Matrices and Vocabulary Scales. HK Lewis; London, UK: 1977.

32. Gunderson KL. Whole-genome genotyping on bead arrays. Methods Mol. Biol. 2009; 529:197–213. [PubMed: 19381978]

33. The International HapMap3 Consortium. Integrating common and rare genetic variation in diverse human populations. Nature. 2010; 467:52–58. [PubMed: 20811451]

34. Marioni RE, Batty GD, Hayward C, Kerr SM, Campbell A, Hocking LJ, et al. Common genetic variants explain the majority of the correlation between height and intelligence: the generation Scotland study. Behav. Genet. 2014; 44(2):91–96. [PubMed: 24554214]

35. Yang J, Benyamin B, McEvoy BP, Gordon S, Henders AK, Nyholt DR, et al. Common SNPs explain a large proportion of the heritability for human height. Nat. Genet. 2010; 42(7):565–569. [PubMed: 20562875]

36. R Core Team. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing; Vienna, Austria: 2012.

37. Purcell, S. PLINK v1.07. http://pngu.mgh.harvard.edu/purcell/plink/

38. Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MAR, Bender D, et al. PLINK: a toolset for whole-genome association and population-based linkage analysis. Am J Hum Genet. 2007; 81(3):559–575. [PubMed: 17701901]

39. Deary IJ. Looking for 'system integrity' in cognitive epidemiology. Gerontology. 2012; 58:545–553. [PubMed: 22907506]

40. Gale CR, Batty GD, Cooper C, Deary IJ. Psychomotor co-ordination and intelligence in childhood and health in adulthood: testing the system integrity hypothesis. Psychosomatic Medicine. 2009; 71:675–681. [PubMed: 19483120]

41. Luciano M, Batty GD, McGilchrist M, Linksted P, Fitzpatrick B, Jackson C, et al. Shared genetic aetiology between cognitive ability and cardiovascular disease risk factors: Generation Scotland's Scottish family health study. Intelligence. 2012; 38:304–313.

42. Starr JM, Taylor MD, Hart CL, Davey Smith G, Whalley LJ, Hole DJ, et al. Childhood mental ability and blood pressure at midlife: linking the Scottish Mental Survey 1932 and the Midspan studies. J. Hypertens. 2004; 22(5):893–897. [PubMed: 15097227]

43. Batty GD, Deary IJ. Early life intelligence and adult health. BMJ. 2004; 329(7466):585–586. [PubMed: 15361422]

44. Davey Smith G, Hemani G. Mendelian randomization: genetic anchors for causal inference in epidemiological studies. Hum Mol Genet. 2014; 23(R1):R89–98. [PubMed: 25064373]

45. Dick KJ, Nelson CP, Tsaprouni L, Sandling JK, Aïssi D, Wahl S, et al. DNA methylation and body-mass index: a genome-wide analysis. Lancet. 2014; 383(9933):1990–1998. [PubMed: 24630777]

46. Lunnon K, Smith RG, Cooper I, Greenbaum L, Mill J, Beeri MS. Blood methylomic signatures of presymptomatic dementia in elderly subjects with type 2 diabetes mellitus. Neurobiol. Aging. 2014 Epub ahead of print.

Table 1

Characteristics of the unrelated genotyped Generation Scotland cohort study members.

		Unrelated Genotyped Cohort	
Variable	n	Mean (SD) or N (%)	Range
Demographics			
Age (years)	6 463	57[*] 49-63	18-98
Sex - Female	6 463	3 783 59	
Body mass index (kg/m^2)	6 463	27.1 4.9	17-50
Cognitive function			
Digit Symbol Test (0-13)	6 379	68.5 16.7	0-133
Verbal Fluency (0-inf)	6 392	41.0 12.1	0-97
Logical Memory (0-50)	6 386	30.3 7.9	0-50
Mill Hill Vocabulary Scale (0-44)	6 353	31.3 4.7	0-44

[*] Median (quartiles).

Table 2

General cognitive function associations with BMI.

General cognitive function	n	Beta[*]	SE	P
Unadjusted association	6 273	−0.11	0.01	$<2.0 \times 10^{-16}$
Adjusted for age and sex	6 273	−0.10	0.01	1.3×10^{-14}

[*] The dependent variable and continuous independent variables were standardised in the regression models.

Table 3

Age-, sex-, and population stratification-adjusted univariate and bivariate GCTA-derived and LDSC-derived estimates.

Univariate estimates	n	est*	SE
General cognitive function			
Same-Sample GCTA	6 273	0.29	0.06
Independent-Samples GCTA	6 985	0.31	0.05
LDSC	48 462	0.15	0.01
BMI			
Same-Sample GCTA	6 463	0.28	0.06
Independent-Samples GCTA	20 806	0.22	0.02
LD Score	339 224	0.14	0.01

Bivariate estimates	N	r_G	SE
Same-sample GCTA	6 273:6 463	−0.51	0.15
Independent-Samples GCTA	6 985:20 806	−0.10	0.08
LD Score	48 462:339 224	−0.22	0.03

BMI: body mass index, r_G: genetic correlation, SE: standard error.

*
The proportion of variance in the phenotype explained by common genetic variants

Table 4

Age- and sex-adjusted polygenic risk score associations with BMI and general cognitive function.

	n	Beta[†]	SE	P
general cognitive function polygenic score [*]				
general cognitive function	6 273	0.090	0.01	3.3×10^{-13}
BMI	6 463	−0.029	0.01	0.020
BMI polygenic score [*]				
general cognitive function	6 273	−0.065	0.01	1.9×10^{-7}
BMI	6 463	0.266	0.01	$<2 \times 10^{-16}$

BMI: body mass index

[*] Polygenic risk scores were adjusted for age, sex, and 14 multi-dimensional scaling components with residuals taken forward as the independent variable of interest.

[†] The dependent variable and continuous independent variables were standardised in the regression models.