Report

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Molecular Genetic Contributions to Social Deprivation and Household Income in UK Biobank

Highlights

- Common SNPs explain 21% of social deprivation and 11% of household income
- Two loci attained genome-wide significance for household income
- Genes in these loci have been linked to synaptic plasticity
- Genetic correlations were found between both measures of SES and many other traits

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In Brief

Individuals with lower socio-economic status (SES) are at increased risk of physical and mental illnesses. Hill et al. find extensive genetic correlations between SES and health, psychiatric, and cognitive traits. This suggests that the link between SES and health is driven, in part, by a shared genetic association.

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Molecular Genetic Contributions to Social Deprivation and Household Income in UK Biobank

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SUMMARY

Individuals with lower socio-economic status (SES) are at increased risk of physical and mental illnesses and tend to die at an earlier age [1–3]. Explanations for the association between SES and health typically focus on factors that are environmental in origin [4]. However, common SNPs have been found collectively to explain around 18% of the phenotypic variance of an area-based social deprivation measure of SES [5]. Molecular genetic studies have also shown that common physical and psychiatric diseases are partly heritable [6]. It is possible that phenotypic associations between SES and health arise partly due to a shared genetic etiology. We conducted a genome-wide association study (GWAS) on social deprivation and on household income using 112,151 participants of UK Biobank. We find that common SNPs explain 21% of the variation in social deprivation and 11% of household income. Two independent loci attained genome-wide significance for household income, with the most significant SNP in each of these loci being rs187848990 on chromosome 2 and rs8100891 on chromosome 19. Genes in the regions of these SNPs have been associated with intellectual disabilities, schizophrenia, and synaptic plasticity. Extensive genetic correlations were found between both measures of SES and illnesses, anthropometric variables, psychiatric disorders, and cognitive ability. These findings suggest that some SNPs associated with SES are involved in the brain and central nervous system. The genetic associations with SES obviously do not reflect direct causal effects and are probably mediated via other partly heritable variables, including cognitive ability, personality, and health.

RESULTS AND DISCUSSION

Using GCTA-GREML [7], we first estimated the heritability of each of the SES variables in the UK Biobank sample. A total of 21% (SE = 0.5%) of phenotypic variation in social deprivation, as measured using Townsend scores, and 11% (SE = 0.7%) of household income was explained by the additive effects of common SNPs. Next, genome-wide association analyses for social deprivation and household income were performed using an imputed dataset that combined the UK10K haplotype and 1000 Genomes Phase 3 reference panels; details can be found at http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=157020. We found no genome-wide significant findings associated with social deprivation (see Figure 1A and Figure S1). For household income, four SNPs attained genome-wide significance ($p < 5 \times 10^{-8}$): rs187848990 on chromosome 2, and rs7252896, rs7255223, and rs8100891 on chromosome 19 (see Figure 1B, Figure S1, and Table S1).

The "clump" function in PLINK [8] was used to identify patterns of linkage disequilibrium in the dataset and showed that these four SNPs were located in two independent regions (Figure 1C). The region on chromosome 2 spanned 583 kb, and the most significant SNP was rs187848990 ($p = 2.325 \times 10^{-8}$). This region contains five genes: *AFF3*, *CHST10*, *LONRF2*, *NMS*, and *PDCL3*. The *AFF3* gene has previously been associated with intellectual disability [9], and *CHST10* is involved with synaptic plasticity [10]. The region on chromosome 19 spanned 18 kb, with the most significant SNP being rs8100891, $p = 3.423 \times 10^{-8}$. This region contains the gene *ZNF507*, which has been implicated in neurodevelopmental disorders including schizophrenia [11], a disorder that affects cognitive function and

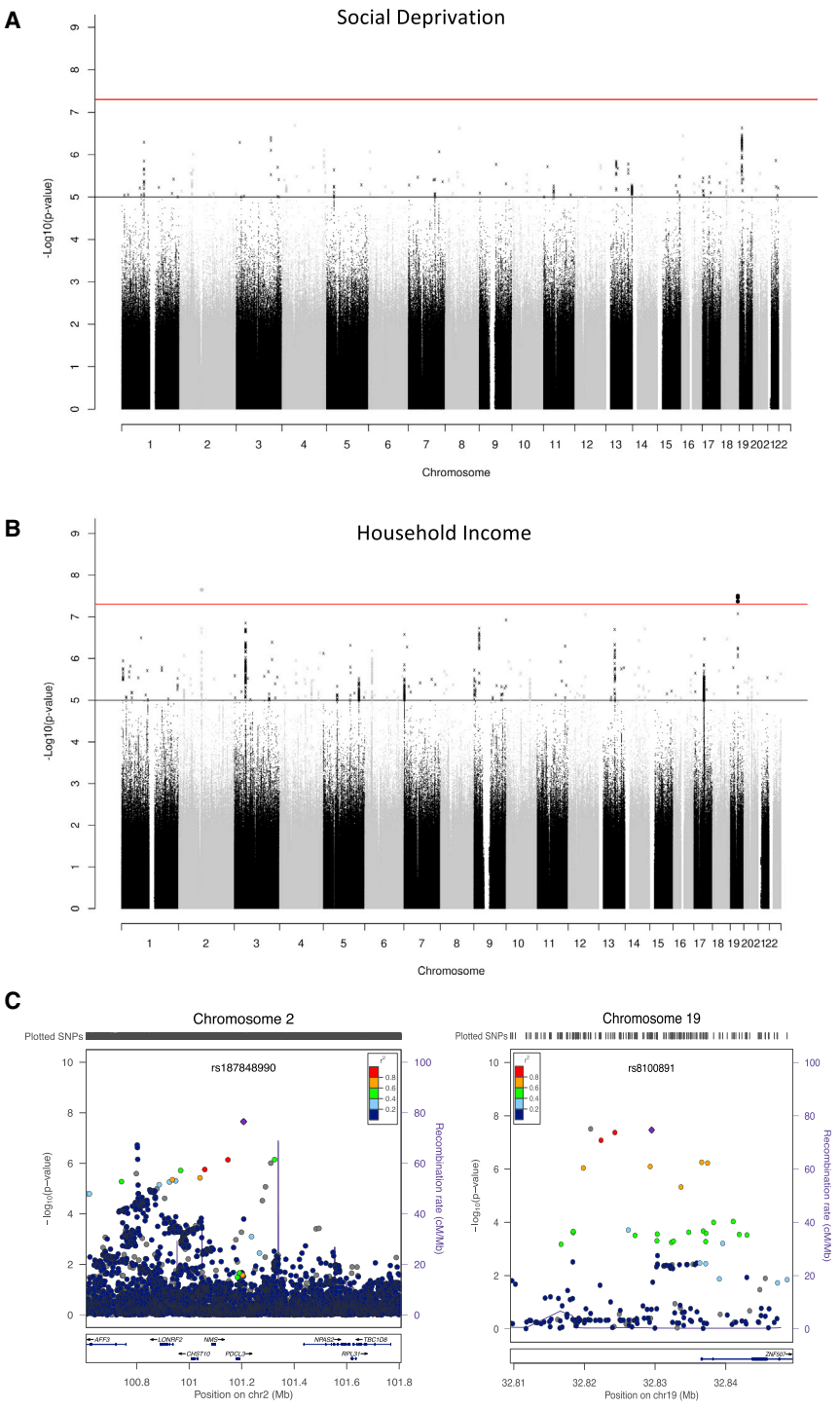

Figure 1. Results of Genome-wide Analysis on Social Deprivation and Household Income

(A) Manhattan plot of $-\log_{10}$ (p values) for social deprivation. The red line indicates genome-wide significance ($p < 5 \times 10^{-8}$). The black line indicates values that were suggestive of statistical significance ($p < 1 \times 10^{-5}$). See also Figure S1.

(B) Manhattan plot of $-\log_{10}$ (p values) for household income. The red line indicates genome-wide significance ($p < 5 \times 10^{-8}$). The black line indicates values that were suggestive of statistical significance ($p < 1 \times 10^{-5}$). See also Figure S1.

(C) Regional association plots for household income of SNPs that attained genome-wide significance ($p < 5 \times 10^{-8}$). rs187848990 is on the left; rs8100891 is on the right. The most significant SNP in these regions is represented with a purple diamond. Each circle represents an individual SNP, and the color indicates pairwise linkage disequilibrium with the most significant SNP in the region (as calculated from 1000 Genomes in November 2014). The solid blue line indicates the recombination rate, and the $-\log_{10}$ p values are shown on the y axis. See also Table S1 and Figures S1–S4.

that shows a strong genetic correlation with intelligence [12]. It is possible, therefore, that these genetic associations with SES may be mediated, in part, through cognitive ability; it is well established that an individual's level of cognitive ability is correlated with their SES [13].

Using the GTEx database (http://www.broadinstitute.org/gtex/), cis-eQTL associations were identified for the four household income genome-wide significant SNPs (Table S1). For this study, data mining of regulatory elements was restricted to normal tissues. There was evidence of regulatory elements associated with all four of the genome-wide significant SNPs (Table S1).

We next sought to replicate the four genome-wide significant SNPs in a sample of ~200,000 individuals who were assessed on the number of years of schooling completed, as this variable is often used as a measure of SES. Summary statistics were made available from the Social Science Genetic Association Consortium's GWAS of educational attainment [14], with data from UK Biobank, UK-based cohorts, and 23andMe being omitted from the analysis. Three of our genome-wide significant SNPs were successfully replicated using years of education as the phenotype, rs187848990 on chromosome 2 ($\beta = 0.066$, $p = 0.047$), and rs7255223 ($\beta = 0.044$, $p = 7.28 \times 10^{-4}$) and rs8100891 ($\beta = 0.044$, $p = 7.62 \times 10^{-4}$) on chromosome 19. rs7252896 was not included in the education data and thus could not be replicated. We then sought to use a SNP that was in high linkage disequilibrium (LD) with rs7252896 to use as a proxy SNP for replication; however, there were no SNPs in the education dataset that were in LD with rs7252896 (r^2 of greater than 0.5), excluding rs7255223 and rs8100891.

We also used this education summary GWAS dataset to derive genetic correlations between both the social deprivation and household income variables in UK Biobank. A genetic correlation of 0.548 (SE = 0.054, $p = 1.796 \times 10^{-24}$) was found between

social deprivation and years of education, and there was a genetic correlation of 0.903 (SE = 0.040, $p = 4.135 \times 10^{-115}$) between income and years of education. These substantial genetic correlations indicate that the two measures of SES, as measured in UK Biobank, have a very similar genetic architecture with a third SES variable—education—measured in an independent sample.

Next, we used polygenic profile scores, derived using the social deprivation and household income variables' GWASs in UK Biobank, to predict social deprivation (using the Scottish Index of Multiple Deprivation, SIMD) and household income in an independent sample, Generation Scotland: Scottish Family Health Study (GS:SFHS) [15, 16]. Polygenic profile scores, calculated using marker weights from the social deprivation GWAS in UK Biobank, produced highly significant associations at each p value threshold with SIMD in GS:SFHS, with the most predictive score being that which was derived using all SNPs ($\beta = 0.079$, SE = 0.008, $r^2 = 0.008$, $p = 2.26 \times 10^{-5}$). Similarly, a polygenic score derived using household income in UK Biobank predicted a significant proportion of phenotypic variance for household income in GS:SFHS at each of the p value thresholds used, with polygenic scores derived using a p value threshold of 0.5 being the most predictive ($\beta = 0.052$, SE = 0.008, $r^2 = 0.003$, $p = 5.07 \times 10^{-11}$). The results of the polygenic profile scores illustrate that the molecular genetic architecture of these SES variables, as measured in the UK Biobank datasets, overlaps with that of GS:SFHS, indicating that the same genetic variants are associated with phenotypic variation in SES in each of these samples. The betas found using the polygenic profile score method predict only a small proportion of the phenotypic variance, which is in line with other phenotypes [17].

Gene-based association testing for the two SES variables in the UK Biobank sample was conducted using MAGMA [18]. Following Bonferroni correction for multiple testing ($\alpha = 2.768 \times 10^{-6}$), gene-based association tests identified one gene associated with social deprivation: *ACCSL* on chromosome 11 ($p = 3.48 \times 10^{-7}$). For household income, 12 genes showed a significant association: *KANSL1* ($p = 8.20 \times 10^{-8}$), *MST1* ($p = 1.10 \times 10^{-7}$), *RNF123* ($p = 1.19 \times 10^{-7}$), *MAPT* ($p = 1.23 \times 10^{-7}$), *APEH* ($p = 2.64 \times 10^{-7}$), *BSN* ($p = 1.03 \times 10^{-6}$), *PLEKHM1* ($p = 1.16 \times 10^{-6}$), *SGCD* ($p = 1.30 \times 10^{-6}$), *DAG1* ($p = 1.55 \times 10^{-6}$), *CRHR1* ($p = 2.39 \times 10^{-6}$), *AMT* ($p = 2.39 \times 10^{-6}$), and *ZDHHC11* ($p = 2.54 \times 10^{-6}$) (Supplemental Experimental Procedures). The *MAPT*, *KANSL1*, *PLEKHM1*, and *CRHR1* genes have been associated with Alzheimer's disease [19].

Partitioned heritability analysis was then conducted on both SES phenotypes in UK Biobank [20]. The goal of the partitioned heritability analysis was to determine whether SNPs that are grouped together, according to a specific biological function or role, make an enriched contribution to the total proportion of heritability for each of the SES variables. The functional categories used here overlap considerably, meaning that the heritability measured by all groups, when they are summed, can exceed 100%. By deriving a heritability estimate for functional classes of SNPs across the genome, a significant enrichment was found for conserved regions of the genome. These conserved regions accounted for 2.6% of the SNPs in both SES phenotypes and accounted for 44% (SE = 12%) of the heritability of social deprivation and 53% (SE = 12%) of the heritability for household income. The trend for enrichment in heritability emanating from such regions is consistent with the results from other quantitative traits and diseases [20] and, as such, further highlights the importance of these genetic regions as sources of phenotypic variance across these complex traits. Under models of neutral selective pressure, these regions accumulate base-pair substitutions at a lower rate than other regions of the genome, indicative of their being regions where mutation results in the production of phenotypic variance susceptible to the effects of purifying selection. Genetic variance within these regions may highlight a role for disease-causing loci, which in turn might account for some phenotypic variance in SES. However, it is also possible that, as intelligence is phenotypically and genetically associated with many health traits [21] and is thought to be evolutionarily selected for [22], these regions may show their association with SES partly through cognitive differences. These two explanations are not mutually exclusive because, after intelligence is included as a covariate, the associations between adult SES and health outcomes, although attenuated, remain significant [1].

Partitioned heritability analysis was also used to conduct a cell-specific analysis of ten broad tissue types (see Supplemental Experimental Procedures). Figure 2 shows the results of cell-specific enrichment for social deprivation and household income. For social deprivation, significant enrichment was found in variants exerting an effect within the central nervous system. Variants expressed in the central nervous system accounted for 15% of the total number of SNPs but accounted for 47% (SE = 11%) of the heritability of social deprivation and 37% (SE = 9%) of the heritability of household income. For household income, this did not survive multiple-testing correction.

We next derived genetic correlations, using linkage disequilibrium score (LDS) regression [23], between both measures of SES and a set of 32 phenotypes that have all been shown in some studies to be phenotypically associated with SES. Table S2 provides references describing examples of the phenotypic associations between measures of SES and broadly conceived health variables. Full details of the GWAS that provided summary statistics for each of the 32 phenotypes, along with links to the data, are also provided in Table S2. The direction of effect for the genetic correlations and polygenic profile scores examining Townsend scores was reversed to facilitate a comparison with the household income variable.

Following false discovery rate (FDR) correction for multiple comparisons, 16 of the 34 genetic correlations were statistically significant for the Townsend social deprivation measure (see Figure 3 and Tables S3), and 24 of the 34 were significant for household income (Figure 4 and Table S3). The large number of genetic correlations found indicates that the molecular genetic associations with SES overlap with many other health-relevant phenotypes. A large degree of overlap was found for variables that are cognitive in nature. Significant genetic correlations were observed, for example, between both measures of SES and childhood cognitive ability (social deprivation, $r_g = 0.500$; income, $r_g = 0.667$), with participants' verbal-numerical reasoning scores in the UK Biobank clinic visit (social deprivation, $r_g = 0.338$; income, $r_g = 0.711$), and also with longevity (social deprivation, $r_g = 0.301$; household income, $r_g = 0.303$). The direction of effect in each instance indicates that more affluent SES is

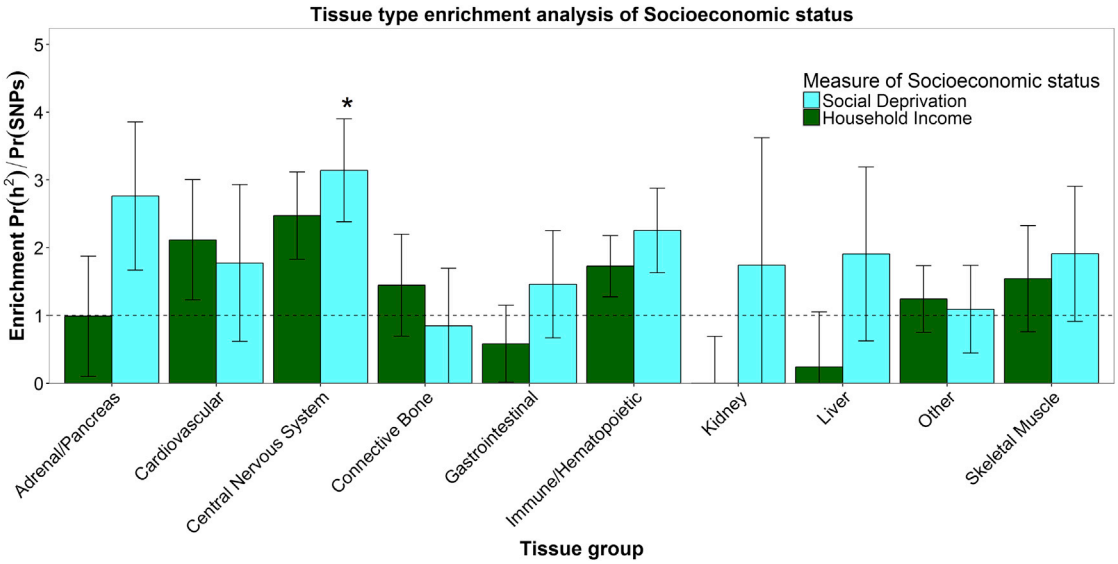

Figure 2. Enrichment Analysis for Social Deprivation and Household Income using the Ten Tissue-Specific Functional Categories

The enrichment statistic is the proportion of heritability found in each functional group divided by the proportion of SNPs in each group: $Pr(h^2)/Pr(SNPs)$. Error bars are jackknife standard errors around the estimate of enrichment. The dashed line indicates no enrichment found when $Pr(h^2)/Pr(SNPs) = 1$. Social deprivation (blue) in only one category was significant, as indicated by an asterisk. No significant enrichment was found for any of the categories considered for the household income (green) phenotype.

associated with longer life and higher intelligence. The average age of the participants in the GWAS for childhood intelligence was 11 years, whereas the measurements of SES from UK Biobank were taken at a mean age of 57 years. The finding of a genetic correlation between these two traits may indicate that a set of genetic variants contributes to higher intelligence, which in turn contributes to a higher SES in mid-life. Significant genetic correlations were found between household income and intracranial volume and infant head circumference (r_g = 0.533 and r_g = 0.239, respectively).

A noteworthy feature of our findings is that the pattern of genetic correlations between our two measures of SES—one area-based and one individual-based—was very similar, and the genetic correlation between the two measures of SES was high, at 0.871 (SE = 0.064). The Townsend social deprivation score is widely used as a proxy indicator of adult socioeconomic status, usually in the absence of an individual measure. It has been shown to be predictive of cancer incidence, all-cause mortality, and other health outcomes [24]. Such area-level effects may comprise both compositional effects, i.e., effects that can be explained in terms of the characteristics of the residents of those areas, and contextual effects, i.e., effects that can be explained in terms of the characteristics of the areas. Although ecological correlations cannot be used to make causal inferences about individuals—the ecological fallacy—it has been suggested that they arise largely from associations at the individual level [25]. One study found that area-based Townsend scores correlate highly with a similar measure of deprivation calculated at the individual level [26]. In our UK Biobank sample, where the individual-level measure of SES was based on household income alone, its correlation with Townsend score was small to moderate in size (r = 0.24); despite this, the pattern of genetic correlations between these two measures was very similar.

There are at least two explanations for the genetic SES-health correlations found using the LDS regression method. The first is that the genetic correlations might have been found as a result of the same genetic variants being directly involved in two phenotypes. The second is the notion of mediated pleiotropy, which describes situations in which a phenotype is causally related to another, perhaps via other variables; therefore, if a genetic variant is associated with the first phenotype, it will be indirectly associated with the second [27]. Should multiple variants be used to establish pleiotropy, such as when using the LDS regression method, both of these forms of pleiotropy may apply, at different loci. However, because SES has no clear biological analog—it describes the environment of an individual or their status within it—mediated pleiotropy thorough intelligence or personality traits such as conscientiousness, for example, would appear to be a much more likely interpretation than biological pleiotropy; that is, we do not conceive of there being genetic variants directly related to SES measures.

The genetic correlations derived in the current paper cannot distinguish the direction of the effect of this shared genetic association between SES and health and cognitive variables. Whereas it is possible that a greater level of cognitive ability will facilitate an individual's ability to move to a higher SES, it could also be the case that those in higher SES environments are exposed to environmental stimuli that facilitate their intellectual development. As both SES and cognitive ability are partly heritable, each of these possibilities would result in a genetic correlation between SES and cognitive ability. Mendelian randomization (MR) is a technique that sits above genetic correlations and polygenic profile scores in the so-called hierarchy of evidence [28] for ascertaining causal inference with regard to how genetic contributions act on exposure and outcomes, as well as for testing the direction of association. However, the data

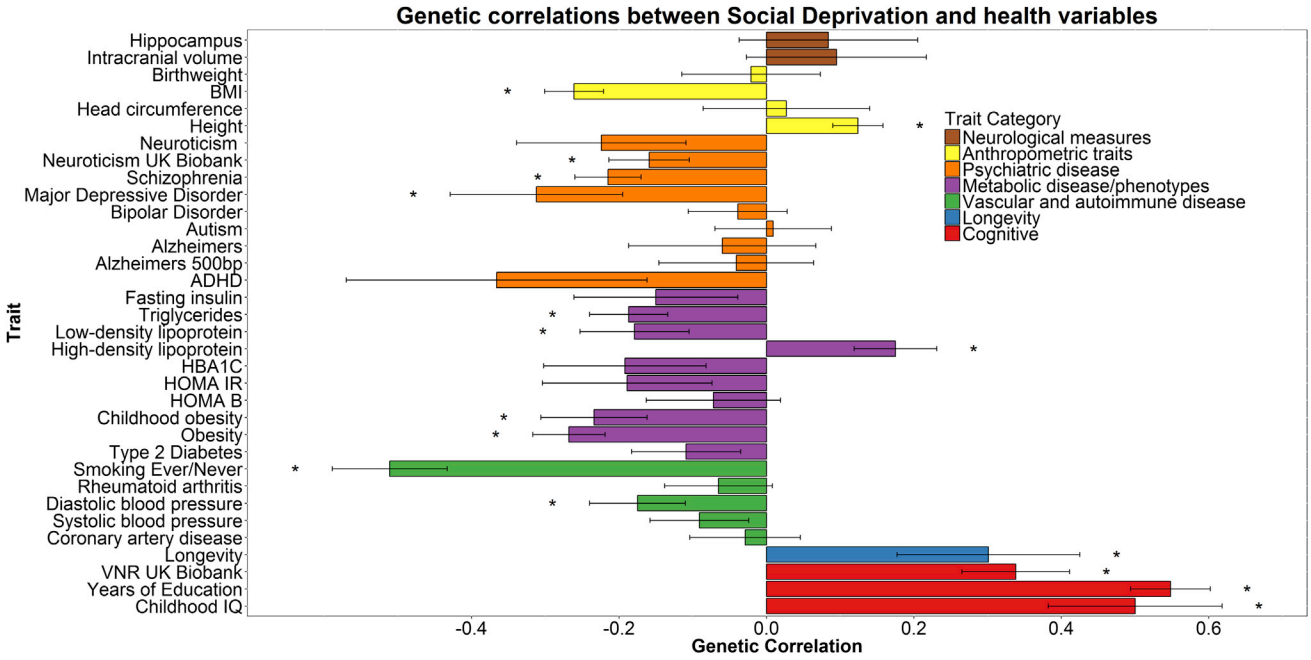

Figure 3. Genetic Correlations between Social Deprivation and Health and Anthropometric Variables

The x axis depicts the magnitude of the genetic correlations; the y axis shows each trait. Statistical significance is indicated by an asterisk. FDR correction indicated statistical significance at p = 0.015. Error bars represent standard error using a ratio block jackknife. HOMA B, homeostatic model assessment β cells; HOMA IR, homeostatic model assessment insulin resistance; HbA1c, glycated hemoglobin; ADHD, attention deficit hyperactivity disorder; MDD, major depressive disorder; BMI, body mass index; ICV, intracranial volume. Social deprivation scores were reversed so that a higher Townsend score indicates a higher SES.

See also Tables S2, S3, and S4.

required to perform these analyses for all traits are not currently available.

The associations between rs187848990 and rs8100891 with household income, along with the heritability estimates for both measures of SES, are, we think, the result of mediation through other phenotypes. Because genetic differences will not directly result in differences in SES, they may be contributing to differences in variables such as intelligence, personality, resistance to diseases, and other factors, which, in turn, can contribute to differences in SES.

The effect sizes found for each individual SNP were small; however, as has been found for other polygenic traits, it is the combined effect of multiple SNPs that contributes to some of the observable phenotypic variance. Polygenic profile scores were created for 28 health-related phenotypes using published GWAS in all participants with genome-wide SNP data. When predicting into social deprivation based on the Townsend score, polygenic profile scores derived from the summary statistics of 11 GWASs of health-related traits predicted a significant proportion of phenotypic variance (Table S4). When predicting into household income, 26 out of 28 demonstrated statistical significance (Table S4). Polygenic profile scores explained only a very small proportion of variance, but they illustrate that genetic risk for a range of diseases and cognitive ability can predict variance in these two SES measures.

As the income variable used in our GWAS pertained to household income, it may have included multiple individuals from the same household. This may have led to individuals providing a phenotype score that did not reflect their own income, but rather the income of those that they lived with. We sought to determine the number of individuals who co-habited in the UK Biobank data and the degree to which this may have influenced the results of the household income GWAS. We omitted one individual per household, retaining the male where possible (Figure S2), which resulted in a reduced sample size of 88,183 individuals who had provided data on their level of household income. Next, we repeated the GWAS, GREML, gene-based analysis, genetic correlations, and the polygenic profile scores. Using this reduced sample in the household income dataset, two additional suggestive peaks were found on chromosome 9, with the most significant SNPs in each of these regions being rs139128645 ($\beta = -0.22$, $p = 1.39 \times 10^{-8}$) and rs7467480 ($\beta = 0.027$, $p = 2.22 \times 10^{-8}$) (Figure S3). The results of the GWAS and the additional analyses were consistent with the likelihood that, by modifying the sample size, there will be minor changes to the test statistics; the results of the GWAS on the full sample for household income and the reduced sample for household income were highly similar. The results did not suggest that a bias had been introduced by there being multiple individuals from a single household. The full results of the reduced-sample GWAS, along with the follow-up analyses, are available from the authors.

The results here show that 21% of people's differences in area-level social deprivation and 11% of household income can be explained by additive common genetic factors. Four genome-wide significant SNPs were found for household income, leading to the identification of two independent genomic

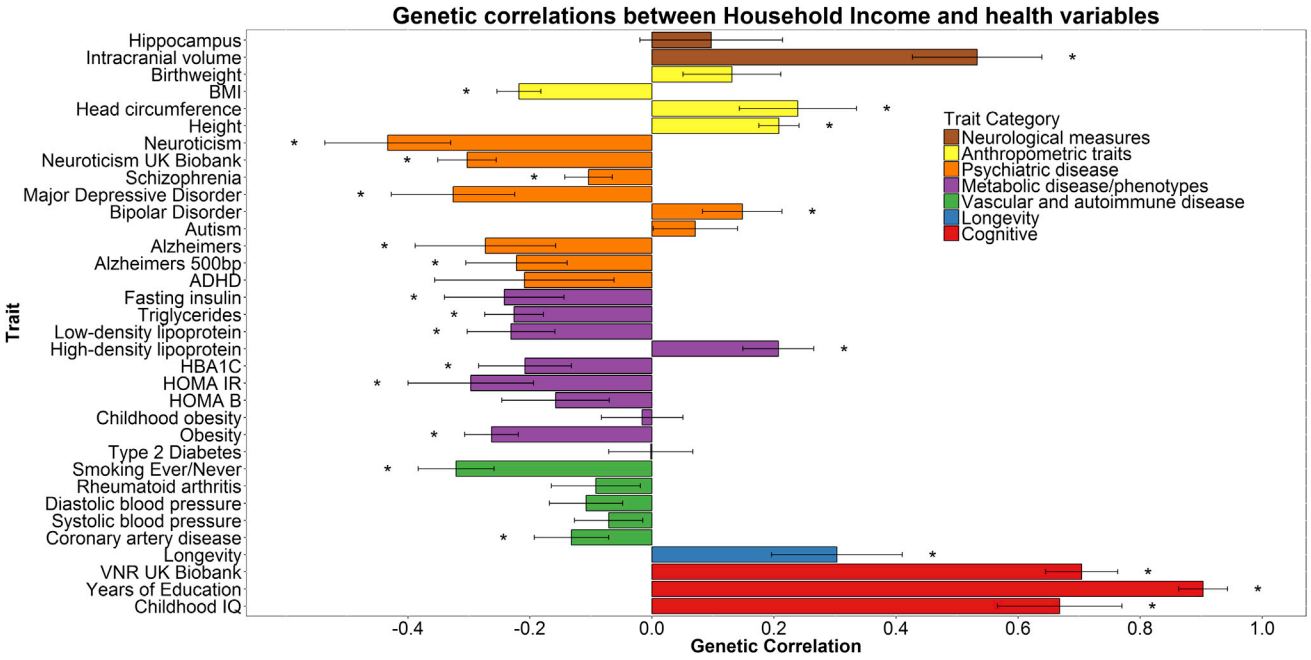

Figure 4. Genetic Correlations between Household Income and Health and Anthropometric Variables

The x axis depicts the magnitude of the genetic correlations; the y axis shows each trait. Statistical significance is indicated by an asterisk. FDR correction indicated statistical significance at p = 0.032. Error bars represent standard error using a ratio block jackknife. HOMA B, homeostatic model assessment β cells; HOMA IR, homeostatic model assessment insulin resistance; HbA1c, glycated hemoglobin; ADHD, attention deficit hyperactivity disorder; MDD, major depressive disorder; BMI, body mass index; ICV, intracranial volume. For household income, higher scores represent higher income.
See also Tables S2, S3, and S4.

regions containing genes with known associations with intellectual disabilities, synaptic plasticity, and schizophrenia. Extensive genetic correlations were found between both measures of SES and health-related traits, indicating a highly diffuse genetic architecture. These genetic correlations might provide a partial explanation for the phenotypic association between SES and health—the majority of which, we think, is due to environmental factors.

EXPERIMENTAL PROCEDURES

We examined two measures of SES that were available in UK Biobank (http://www.ukbiobank.ac.uk) [29]. The first measure was the Townsend Social Deprivation Index [30]—a measure of the level of social deprivation in which the participant lives—and the second measure was household income. A total of 112,005 individuals had a Townsend score, of whom 52.53% were female (mean age = 56.91 years, SD = 7.93, range 40–73). A total of 96,900 participants had data pertaining to household income, of whom 50.64% were female (mean age = 56.53 years, SD = 7.95, range 40–73). Participants had undergone genome-wide SNP genotyping; the full details of this can be found in the Supplemental Experimental Procedures.

We used data from the UK Census of 2001 (https://census.ukdataservice.ac.uk/media/215850/Townsend2001.csv) and compared the distribution of Townsend scores from all of England and Wales to those in UK Biobank that had been genotyped. The data from the UK census exclude wards of less than 100 households, which only altered wards in the City of London and the Scilly Isles. The score was first reversed so that a greater Townsend score corresponds to a higher SES. As can be seen in Figure S4, the distribution of the Townsend score from the UK Biobank dataset follows the same trend as that found across England and Wales. This indicates that, whereas those from very low SES environments—corresponding to a Townsend score of less than −10—did not participate in UK Biobank, the distribution of scores is highly similar to what was found across England and Wales (UK Biobank median = 2.3, census of 2001, median = 1.1). The distribution of the income scores can be found in Figure S4.

We conducted separate analyses for the Townsend deprivation score and household income. All phenotypes were adjusted for age, gender, assessment center, genotyping batch, genotyping array, and ten principal components in order to correct for population stratification prior to all analyses. See Supplemental Experimental Procedures for full description of genotyping, imputation, and the phenotypes used.

SUPPLEMENTAL INFORMATION

Supplemental Information includes Supplemental Experimental Procedures, four figures, and four tables and can be found with this article online at http://dx.doi.org/10.1016/j.cub.2016.09.035.

AUTHOR CONTRIBUTIONS

Conceptualization, W.D.H., C.R.G., I.J.D.; Software, D.C.M.L., G.D.; Formal Analysis, W.D.H., S.P.H., R.E.M., G.D.; Data Curation, W.D.H., S.P.H., S.E.H.; Writing – Original Draft, W.D.H., as discussed with I.J.D.; Writing – Review and Editing, W.D.H., S.P.H., R.E.M., S.E.H., D.C.M.L., G.D., A.O., A.M.M., C.R.G., I.J.D.

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Supplemental Information

Molecular Genetic Contributions to Social Deprivation and Household Income in UK Biobank

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Supplemental Figures and Tables

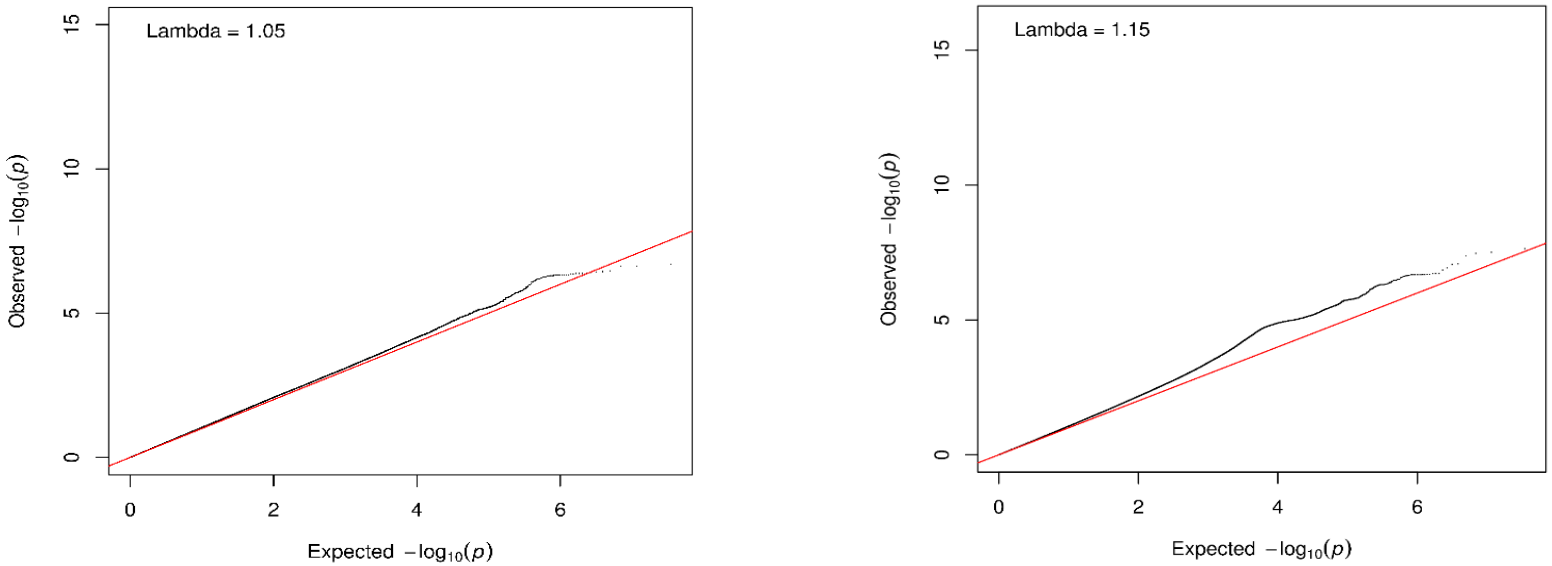

Figure S1. Related to Figure 1. Q-Q plot of social deprivation (left panel) shows that the distribution of $-\log_{10} P$-values follows that which would be expected under the null hypothesis. Q-Q plot of household income (right panel) shows that the distribution of $-\log_{10} P$-values indicates more low P-values than would be expected under the null hypothesis.

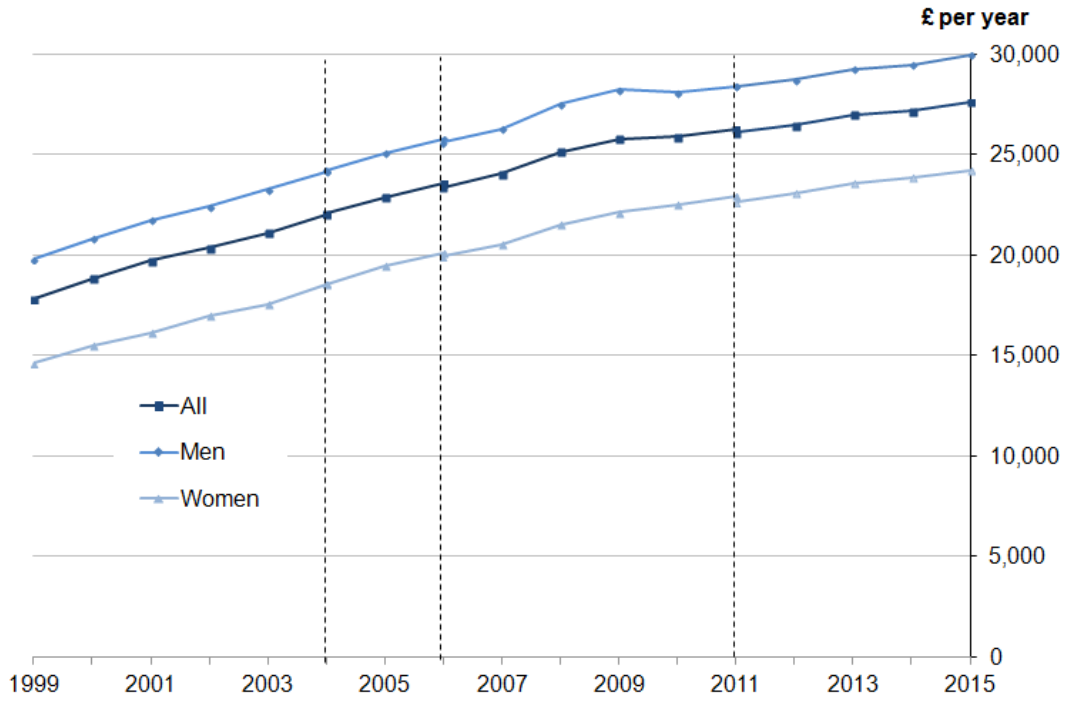

Figure S2. Related to Figure 1. Median full-time gross annual earnings by sex in the UK from 1999 to 2015.

Employees employed for greater than one year and were working full timed defined as greater than 30 hours per week, or 25 for teaching professions. Dashed line indicates discontinuities in the estimates of the Annual Survey of Hours and Earnings.

Figure taken from the Office for National Statistics (http://www.ons.gov.uk/employmentandlabourmarket/peopleinwork/earningsandworkinghours/bulletins/annualsurveyofhoursandearnings/2015provisionalresults#gender-pay-differences).

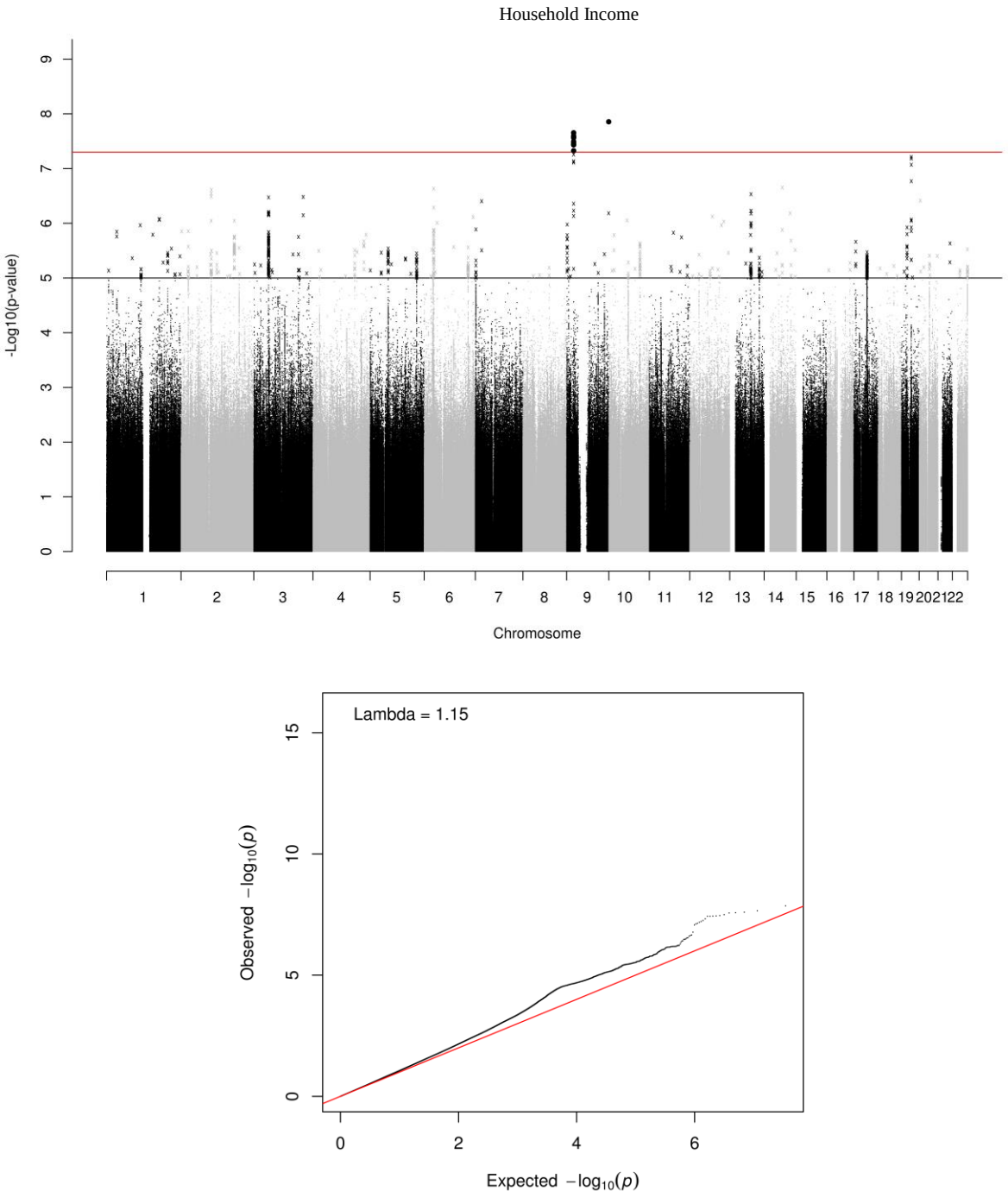

Figure S3. Related to Figure 1. Manhattan and Q-Q plot of the reduced sample size of 88,183. The upper panel shows the Manhattan plot for household income using. The red line indicates genome wide significance ($P < 5 \times 10^{-8}$). The black line indicates values that were suggestive of statistical significance ($P < 1 \times 10^{-5}$). The lower panel shows the Q-Q plot and shows that the distribution of $-\log_{10} P$-values indicates more low P-values than would be expected under the null hypothesis.

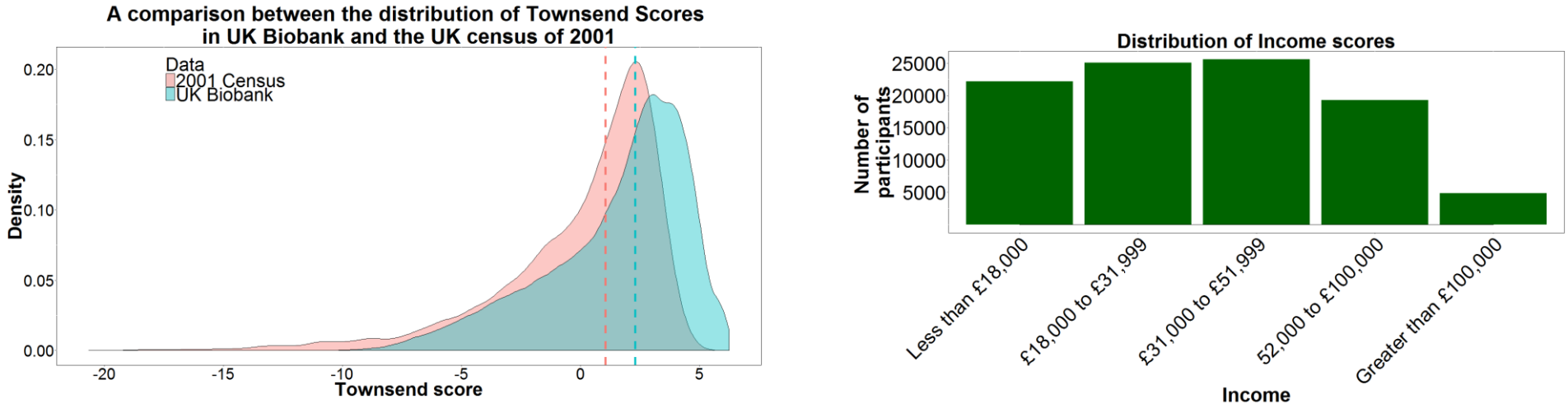

Figure S4. Related to Figure 1. The panel on the left shows the distribution of scores from the Townsend scores in UK Biobank with those taken from the national census in 2001 in England and Wales. The scores form each phenotype have been reversed so that a greater score indicates a greater SES. The similarity of these two distributions indicates that the UK Biobank data set is comparable to the rest of the UK. The panel on the right shows the distribution of the Income scores in UK Biobank. This indicates that most of the participants were in households where the income was between £18,000 to £31,999 and £31,000 to £51,999.

Table S1. Related to Figure 1B. Genome-wide significant SNP-based association results for household income ($P < 5 \times 10^{-8}$). The results are ordered by significance of the association. The independent SNP signals, as determined by the LD Clumping analysis, are highlighted in red. The sample size was 96,900 for each SNP presented below. Functional annotation of the household income associated genome-wide significant SNPs. All information contained in this table was extracted from the GTEx database (http://www.broadinstitute.org/gtex/) and the Regulome DB database (http://regulome.stanford.edu/index).

SNP number	Chr	Position	Allele 1	Allele 2	*P*-value	Beta	MAF	INFO	cis-eQTL	Regulome DB Score	Position weight matrix	Transcription factor binding site	Histone modifications	DNase hyper sensitive sites	FAIRE sites	DMR
rs187848990	2	101207261	T	C	2.23×10^{-8}	0.077	0.030	0.945	no	6	yes	no	yes	no	no	no
rs7252896	19	32820876	A	T	3.11×10^{-8}	0.030	0.247	0.924	no	6	yes	no	yes	no	no	no
rs8100891	19	32829513	G	C	3.42×10^{-8}	0.029	0.261	0.998	yes	5	yes	yes	yes	no	no	no
rs7255223	19	32824310	A	C	4.27×10^{-8}	0.028	0.263	0.995	yes	4	no	yes	yes	yes	no	no

Table S3. Related to Figure 3 and Figure 4. Genetic correlations between SES as measured by social deprivation and household income from UK Biobank and the 32 health and anthropometric variables. The heritability Z-score and the mean χ^2 indicate the level of power to detect association where a heritability Z-score of >4 and a mean χ^2 >1.02 being considered well powered [S47]. Tests that withstood FDR correction are shown in bold. FDR correction indicated statistical significance at $P = 0.0153$ for social deprivation and at $P = 0.032$ for household income.

	Social Deprivation					Household Income				
Phenotypes	**Genetic correlation**	**Standard error**	***P*-value**	**Heritability Z-score**	**Mean χ^2**	**Genetic correlation**	**Standard error**	***P*-value**	**Heritability Z-score**	**Mean χ^2**
Cognitive abilities										
Childhood intelligence	0.500	0.118	**2.30×10^{-5}**	5.942	1.076	0.668	0.102	**4.96×10^{-11}**	5.8616	1.076
Years of Education	0.548	0.054	**1.80×10^{-24}**	20.687	1.372	0.903	0.040	**4.14×10^{-115}**	20.687	1.372
VNR Biobank	0.338	0.073	**3.80×10^{-6}**	10.865	1.167	0.704	0.059	**3.94×10^{-33}**	10.481	1.167
Longevity										
Longevity	0.301	0.1242	**0.0154**	4.127	1.038	0.303	0.107	**0.005**	4.049	1.038
Vascular and autoimmune disease										
Coronary artery disease	−0.029	0.075	0.700	7.954	1.145	−0.132	0.061	**0.032**	7.890	1.145
Systolic blood pressure	−0.091	0.067	0.175	12.507	1.048	−0.071	0.056	0.204	12.172	1.048
Diastolic blood pressure	−0.175	0.065	**0.007**	11.519	1.051	−0.108	0.060	0.073	10.677	1.051
Rheumatoid arthritis	−0.065	0.073	0.377	3.691	1.064	−0.092	0.073	0.205	3.814	1.064
Smoking yes/no	−0.511	0.078	**5.87×10^{-11}**	11.358	1.104	−0.321	0.062	**2.11×10^{-7}**	11.358	1.104
Metabolic disease/phenotypes										
Type 2 Diabetes	−0.109	0.074	0.143	9.066	1.133	−0.002	0.069	0.972	9.001	1.133
Obesity	−0.268	0.049	**3.23×10^{-8}**	17.370	1.124	−0.263	0.044	**2.11×10^{-9}**	17.556	1.124
Childhood obesity	−0.234	0.072	**0.001**	9.261	1.033	−0.016	0.067	0.809	9.357	1.033
HOMA B	−0.072	0.091	0.430	6.605	1.053	−0.158	0.088	0.073	6.145	1.053
HOMA IR	−0.189	0.115	0.101	5.342	1.053	−0.297	0.103	**0.004**	5.252	1.053

HbA1c	−0.192	0.110	0.081	5.410	1.060	−0.208	0.076	**0.006**	5.291	1.060
High density lipoprotein cholesterol	0.175	0.056	**0.002**	5.535	1.152	0.207	0.058	**3.48×10^{-4}**	5.546	1.152
Low density lipoprotein cholesterol	−0.179	0.074	**0.015**	3.717	1.140	−0.231	0.072	**0.001**	3.585	1.140
Triglycerides	−0.187	0.053	**4.30×10^{-4}**	5.931	1.153	−0.226	0.048	**2.47×10^{-6}**	5.937	1.153
Fasting insulin	−0.150	0.111	0.175	5.814	1.054	−0.242	0.098	**0.014**	5.867	1.054
Psychiatric disease										
ADHD	−0.366	0.204	0.073	2.297	1.016	−0.209	0.147	0.156	2.420	1.016
Alzheimer's 500kb	−0.041	0.105	0.698	5.531	1.105	−0.222	0.083	**0.007**	5.365	1.105
Alzheimer's	−0.060	0.127	0.636	2.127	1.114	−0.273	0.115	**0.018**	1.917	1.114
Autism	0.009	0.079	0.913	8.759	1.058	0.071	0.069	0.302	8.485	1.058
Bipolar	−0.039	0.067	0.558	10.591	1.186	0.148	0.065	**0.024**	10.405	1.186
MDD	−0.312	0.117	**0.007**	5.474	1.078	−0.326	0.101	**0.001**	5.520	1.078
Schizophrenia	−0.215	0.045	**1.66×10^{-6}**	22.285	1.812	−0.104	0.039	**0.009**	22.202	1.812
Neuroticism UK Biobank	−0.159	0.054	**0.003**	9.121	1.239	−0.303	0.048	**3.92×10^{-10}**	9.090	1.239
Neuroticism	−0.224	0.115	0.051	4.199	1.057	−0.433	0.103	**2.85×10^{-5}**	4.334	1.057
Meta−Neuroticism			**9.06×10^{-4}**							
Anthropometric traits										
Height	0.124	0.034	**3.00×10^{-4}**	17.958	2.973	0.208	0.033	**1.51×10^{-10}**	17.766	2.973
Head circumference	0.027	0.113	0.810	5.492	1.041	0.239	0.096	**0.013**	5.311	1.041
BMI	−0.261	0.040	**7.83×10^{-11}**	18.081	1.262	−0.218	0.036	**9.62×10^{-10}**	18.765	1.262
Birthweight	−0.021	0.094	0.826	6.109	1.062	0.131	0.080	0.102	5.735	1.062
Neurological measures										
ICV	0.095	0.122	0.438	3.819	1.041	0.533	0.106	**4.79×10^{-7}**	3.745	1.041
Hippocampal volume	0.084	0.121	0.486	3.655	1.024	0.097	0.117	0.407	3.736	1.024

Abbreviations: HOMA B, homeostatic model assessment beta-cells; HOMA IR, homeostatic model assessment insulin resistance; HbA1c, glycated haemoglobin; ADHD, attention deficit hyperactivity disorder; MDD, major depressive disorder; BMI, body mass index; ICV, intracranial volume.

Supplemental Experimental Procedures

Study design and participants

The principal data set used in this study of socioeconomic status (SES) was taken from UK Biobank (http://www.ukbiobank.ac.uk) [S48]. UK Biobank consists of 502,655 community-dwelling participants recruited between 2006 and 2010 in the United Kingdom (target age range 40-69 years). Participants gave detailed information about their background and lifestyles, underwent cognitive and physical tests, and agreed to have their health followed longitudinally. In addition, blood, urine, and saliva samples were provided for future analyses. In the current study, genome-wide genotyping data were available on 112,151 individuals (52.53% female) aged 40-73 years (mean age = 56.9 years, SD = 7.9) after the quality control process was implemented (described below). UK Biobank received ethical approval from the Research Ethics Committee (REC) (REC reference, 11/NW/0382). This study has been completed under UK Biobank application 10279.

Phenotype measurement of SES

Two measurements of SES were used in the current study. An area based measurement, The Townsend Social deprivation Index [S49], and self-reported household income. The Townsend score is a measure of the level of social deprivation for the area in which the individual lives. Each participant was assigned a Townsend score at the time of recruitment. Data from the last national census were used to derive the score for each participant based on their postcode. Four variables contribute to a participant's Townsend score: the percentage of those aged 16 or over who are unemployed, and percentages of households who do not own a car, do not own their home, and which are overcrowded. The Townsend score is an indicator of the level of social deprivation in an area, where a greater score indicates a higher level of deprivation and a lower average SES.

Self-reported household income was collected using a 5 point scale corresponding to the total household income before tax, 1 being less than £18,000, 2 being £18,000 - £29,999, 3 being £30,000 - £51,999, 4 being £52,000 – £100,000, and 5 being greater than £100,000. Participants were removed from the analysis if they answered "do not know" (n= 4319), or "prefer not to answer" (n = 10553).

In response to a reviewer's request, we investigated the degree to which multiple individuals from the same household may have contributed to UK Biobank. It should be noted that the data pertaining to participant

co-habitation is based on address and so individuals who reside in the same army barracks, care homes, hospitals etc, would count as living together. In addition these data do not take into account any changes of address since recruitment, nor the how long participants have been living in the same address. We removed one individual per household retaining the male if available in order to more closely pair the phenotype (household income) with the genotype more likely to contain causal elements, Figure S2. This resulted in a final sample size of 88,183 (47,797 males and 40,386 females). We then repeated the GWAS on this reduced data set along with the gene-based analysis, genetic correlations, and polygenic profile scores.

Genotyping and Quality Control

The 152,729 blood samples submitted to UK Biobank were genotyped using either the UKBileve array (N = 49,979) or the UK Biobank axiom array (N = 102,750). Affymetrix performed genotyping on 33 batches of ~4,700 samples and also conducted the initial quality control procedure on the genotyping data. Details of the sample processing specific to the UK Biobank project are available at http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=155583, and the details of the Axiom array at http://media.affymetrix.com/support/downloads/manuals/axiom_2_assay_auto_workflow_user_guide.pdf.

Prior to release of data from UK Biobank, a stringent quality control protocol was applied, and performed at the Wellcome Trust Centre for Human Genetics (WTCHG). Further details of the quality control procedure implemented by the WTCHG can be found at http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=155580.

Additional quality control was performed for this study. Individuals were removed based on non-British ancestry (within those who self-identified as being British, principal component analysis was used to remove outliers, *n*=32,484), high missingness (*n*=0), relatedness (*n*=7,948), QC failure in UK Bileve (*n*=187), and gender mismatch (*n*=0). A total of 112,151 individuals remained for further analyses.

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

The UK Biobank interim release was imputed to a reference set which combined the UK10K haplotype and 1000 Genomes Phase 3 reference panels. Full details can be found at http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=157020. The association results were filtered to exclude variants where minor allele frequency (<0.1%) or imputation quality (<0.1) leaving a total of ~17.3 million SNPs.

Curation of summary data from GWAS on physical and psychiatric disease

Genetic correlations and polygenic profile scores were derived using the SES variables in UK Biobank and summary statistics from 32 mostly health-related phenotypes which show phenotypic correlations with SES. Table S2 provides key references showing evidence for the phenotypic associations between measures of SES and health. Full details of the prior GWAS studies which provided summary statistics along with links to the data (where applicable) are provided in Table S2.

Statistical Analysis

Genome-wide SNP-based heritability

The total phenotypic variance explained by common SNPs was estimated using GCTA-GREML [S50, S51]. All genotyped autosomal variants were included in the GCTA-GREML analyses for both the social deprivation and the household income variables from UK Biobank.

SNP-based association analyses

Association analyses for both the social deprivation phenotype and the household income phenotype were adjusted to control for the effects of age, sex, assessment centre, genotyping batch, genotyping array, and population stratification (using 10 principal components). A total of 112,005 participants had both a Townsend score and genotype data available and a total of 96,900 genotyped individuals provided data on household income. Association analyses were conducted using SNPTEST v2.5 [S52] (software available at https://mathgen.stats.ox.ac.uk/genetics_software/snptest/snptest.html#introduction). An additive model was used by specifying the 'frequentist1' option and genotype dosage scores were used to account for imputed genotype uncertainty.

Clumping

The degree to which genome-wide significant hits were tagging independent regions of the genome was examined by using linkage disequilibrium (LD) clumping in PLINK. Here, the European panel of the 1000 genomes (phase 1, release 3) was used to model the degree of LD between markers. Index SNPs, defined as those with a *P*-value of $< 5 \times 10^{-8}$, SNPs within 500kb of the index SNP and in LD of $r^2 > 0.1$ and with a *P*-value of $< 1 \times 10^{-5}$, were used to define genomic regions.

Gene-based association analysis

Gene-based association analyses were conducted using MAGMA [S53]. Summary data from the SNP-based analyses were used to derive gene-based statistics. SNPs were allocated to genes based on their position according to the NCBI 37.3 build with gene boundaries being defined as the start and stop site. The European panel of the 1000 genomes (phase 1, release 3) was used to model linkage disequilibrium. This resulted in a total of 18,061 genes being included in the gene-based analysis for social deprivation and for household income. A Bonferroni correction was used to control for multiple testing, giving an alpha level for social deprivation and for household income of 2.768×10^{-6}.

Functional annotation and gene expression

For the four genome-wide significant SNPs associated with household income (reported below), evidence of expression quantitative trait loci (eQTL) and functional annotation were explored using publicly-available online resources. The Genotype-Tissue Expression Portal (GTEx) (http://www.gtexportal.org) was used to identify eQTLs associated with the SNPs. Regulome DB [S54]. (http://www.regulomedb.org/) was used to identify regulatory DNA elements in non-coding and intergenic regions of the genome in normal cell lines and tissues.

LDS regression partitioned heritability method

Partitioned heritability can be achieved using the LDS regression method [S55]. This analysis examines groups of SNPs that share the same functional properties and is used to derive a heritability metric for each grouping. The goal of these analyses is to determine if specific groups of SNPs make a greater contribution to the total heritability estimate than would be expected by their size. This is achieved by performing multiple regression of GWAS test statistics onto LD scores for partitioned regions of the genome. This enables the percentage of a trait's total SNP-based heritability for specific regions of the genome to be derived. In order to show that a region of the genome is making a greater contribution to a phenotype than would be expected, an enrichment statistic is derived. Here enrichment is defined as the proportion of the heritability of the region, divided by the proportion of SNPs contained within it or $Pr(h^2)/Pr(SNPs)$. Should $Pr(h^2)/Pr(SNPs) = 1$, no enrichment is found, as the proportion of SNPs a region contains is equal to the heritability it tags. In instances

where $Pr(h^2)/Pr(SNPs) > 1$ the region shows evidence that it is making a greater contribution towards the heritability estimate than its size alone would suggest.

Enrichment of partitioned regions was performed separately for social deprivation and household income. Firstly a baseline model was derived using 52 overlapping, functional categories (described below). Secondly, a cell-specific model was constructed by adding each of the 10 cell-specific functional groups to the baseline model one at a time.

Multiple testing was controlled for by applying an FDR correction to the to the baseline model using 52 categories. For the cell-specific analysis the baseline model was first included and the level of enrichment for each cell specific category as derived. Here, 10 tests were controlled for using FDR.

A total of 52 overlapping categories were included in the baseline model. These were coding regions, 3'UTR, 5'UTR, promoter and intronic regions [S56, S57]. The gene sets of digital genomic footprint and transcription factor binding site were used [S57, S58]. The CTCF, promoter-flanking, transcribed, transcription start sites (TSS), strong enhancer and weak enhancer categories are included [S59]. DNase I hypersensitivity sites (DHS) were formed by utilising the data from ENCODE and from the Roadmap Epigenomes data [S60]. These were used to create two functional groups, one corresponding to all cell types and the second only those that were found within the foetal cell type. Cell type specific H3K4me1, H3K4me3, and H3K9ac data were taken from work performed on the Epigenomics Roadmap [S34]. An additional version of H3k27ac was also included [S61]. For each of these groups all cell types were used in the baseline model. Super enhancers are clusters of enhancers that show a high level of activity [S61]. This group correspond to a subset of the H3K27 annotation. Also included is a group that has been shown to be conserved along the mammalian line [S62, S63]. Finally, a group of enhancers were included that show a bidirectional capped transcript. These were identified using cap analysis of the gene expression levels in the sample panel of FANTOM5 [S64]. In order to control for SNPs within these categories tagging variance coming from outside the groupings a 500 kb boundary was included around each category and a 100bp window around the ChIP-seq peaks (regions that were DNase hypersensitive or associated with the H3K4me1, H3K4me, or the H3K9ac groupings).

The SNPs in the baseline histone mark groupings were formed by combining across tissue types. In order to determine if specific tissue types make greater contributions to SES we grouped each mark into cell

types of central nervous system, kidney, liver, cardiovascular, connective/bone, gastrointestinal, immune/hematopoietic, adrenal/pancreas, skeletal muscle, and other.

Genetic overlap with other traits

Genetic correlations can be derived by exploiting the pattern of LD found across the genome. This is due to the level of association a SNP shows in a GWAS is a product of both its own contribution toward a phenotype as well as variants that it is in LD with [S65]. In addition, SNPs in regions of high LD provide a measure of a greater proportion of the genome than SNPs in regions of low LD.

Assuming a polygenic architecture, SNPs in regions of high LD will show greater association statistics than SNPs found in regions of low LD. This means that the level of LD can be used to predict GWAS association test statistics [S47, S66]. By extending this logic to a bivariate design, the product of test statistics from each locus can be predicted using LD in the presence of a non-zero genetic correlation between pairs of traits.

Here, we use LDS regression to derive genetic correlations between SES, as measured by the Townsend Social Deprivation Index [S49] and household income, and health traits using 32 large GWAS consortia data sets to quantify the level of overlap between the genetic architecture of health traits and SES in UK Biobank. This method has been used before to establish a shared genetic component between cognitive functions and health traits [S47, S67, S68]. With regard to the analyses using the summary data from the Alzheimer's disease GWAS, due to the large effects in the *APOE* region, a 500kb region was removed from around each side of this region and the analysis was repeated. The Alzheimer's data set without this region is referred to as Alzheimer's 500kb in the Tables S3. Due to the high genetic correlation between the two measures of neuroticism used ($r_g = 1$), the *P* values derived from the genetic correlations between these two variables with social deprivation were meta-analysed using Stouffer's weighted *Z* [S69, S70]. This meta-analysed *P* value was then used to test whether statistical significance remained following FDR control for the tests performed.

We use the data processing pipeline described by Bulik-Sullivan et al., (2015) [S47] to derive genetic correlations between pairs of traits. A MAF of > 0.01 was used as a cut off and only those SNPs found in the HapMap3 with 1000 Genomes EUR with a MAF > 0.05 were included. The integrated_phase1_v3.20101123 was used for LDS regression. Next, indels and structural variants were removed, as were strand-ambiguous SNPs. Genome-wide significant SNPs were also removed, along with SNPs with very large effect sizes ($\chi^2 > 80$)

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 prediction

The .map and .ped files supplied by UK Biobank were recoded to the ACGT format (from the 1, 2 numerical allele code) using a bespoke program developed by one of the authors (DCL). This program used the look-up substitution method where by a look up string hash table was created to hold the SNP-ID in addition to the allele identifiers for the SNP. A loop was conducted on the string position which created an additional string with the correct ACGT encode. This was then included to the six mandatory fields extracted from the initial string.

Polygenic profile scores were created for 28 health-related phenotypes from published GWAS in all participants with genome-wide SNP data using PRSice [S71]. Strand-ambiguous SNPs and SNPs with a minor allele frequency < 0.01 were removed prior to creating the polygenic profile scores. SNPs in linkage equilibrium with an $r^2 < 0.25$ within a 200bp window were obtained using clumping. The polygenic profile scores were then calculated by the sum of the alleles associated with the phenotype of interest across many genetic loci, weighted by their effect size estimated from the GWAS summary statistics. Five polygenic profile scores were created including variants according to the significance of their association with their phenotype, at *P*-value thresholds of 0.01, 0.05, 0.1, 0.5 and all SNPs.

The associations between the 28 polygenic profile scores and SES were examined using regression models, adjusting for age at measurement, sex, genotyping batch, genotyping array, assessment centre, and the first ten genetic principal components to adjust for population stratification. All analyses were performed in R, and all obtained *P*-values were corrected for multiple testing using the False Discovery Rate (FDR) method [S72].

A number of the data sets used in the analysis incorporating LDS regression were unsuitable for use with the polygenic profile score method and so the phenotypes of, HDL, LDL, and triglycerides had to be omitted from polygenic score analysis. In addition, the polygenic profile score method cannot be used in situations where there is sample overlap. Because of this, phenotypes within UK Biobank could not be compared with each other using this method. Sample overlap may have occurred between the GWAS consortia

used to establish genetic correlations between SES and health variables as participants from the UK were used. However, there is currently no method to quantify the degree to which this may have occurred, and therefore some of the polygenic profile scores results should be interpreted with caution. The genetic correlations are, however, robust to sample overlap [S47].

Replication

The genome wide significant SNPs from the GWAS on household income in UK Biobank were tested for replication into another measure of SES, years of education using an independent sample of ~200,000 individuals [S3]. Years of education was measured as the number of years of schooling completed. The data provided by The Social Science Genetic Association Consortium [S3] did not contain data from 23andMe or from UK Biobank, or any of the UK based cohorts. rs7252896 was not included in the years of education data and no SNPs were found with an r^2 of greater than 0.5 that were not amongst the genome wide significant SNPs from UK Biobank.

In order to further examine the degree to which the genetic architecture of social deprivation and household income as measured in the UK Biobank data set overlapped with that of years of education assembled by The Social Science Genetics Association Consortium we used Linkage Disequilibrium Score regression to derive genetic correlations. The same data processing pipeline was used as described above.

Next, using PRSice [S71], we derived polygenic profile scores using the summary statistics from the social deprivation and household income GWASs in UK Biobank and used these scores to predict social deprivation and household income in Generation Scotland: the Scottish Family Health Study (GS:SFHS) data set [S73, S74, S75]. Social deprivation was measured in GS:SFHS using the Scottish Index of Multiple Deprivation 2009 (SIMD, http://www.scotland.gov.uk/topics/statistics/simd/). In brief this measure takes small areas of Scotland which are then ranked according to seven categories each indicating SES. These are income, employment, health, education, geographic access, crime, and housing. The scores derived using the SIMD are ranked the most deprived, 1, to areas that are the least deprived 6505. Household income in GS:SFHS was measured by multiple choice where the possible answers were 1 less than £10,000, 2 between £10,000 and £30,000, 3 between £30,000 and £50,000, 4 between £50,000 and £70,000, 5 more than £70,000, and 6 prefer not to answer [S74, S75]. Individuals who responded with 6 "prefer not to answer" were excluded from the analysis. Individuals were removed if they had contributed to both GS:SFHS and UK Biobank (N = 174). Linear regression models were used to examine the associations between the polygenic profiles for the UK Biobank

household income and Townsend and the target phenotypes in GS:SFHS, adjusted for age at measurement, sex and the first five genetic principal components for population stratification. All models were corrected for multiple testing across all polygenic profile scores at all five thresholds in each cohort using the False Discovery Rate method [S76].

Using marker weights from the social deprivation GWAS in UK Biobank, highly significant associations at each *P*-value threshold with SIMD in GS:SFHS where found. The most predictive score being that which was derived using the all SNPs, (*P*-value threshold = 0.01, Beta = 0.033, SE = 0.008, r^2 = 0.001, *P* = 2.26×10^{-5}, *P*-value threshold = 0.05, Beta = 0.065, SE = 0.008, r^2 = 0.005, *P* = 2.26×10^{-5}, *P*-value threshold = 0.1, Beta = 0.072, SE = 0.008, r^2 = 0.007, *P* = 2.26×10^{-5}, *P*-value threshold = 0.5, Beta = 0.077, SE = 0.008, r^2 = 0.008, *P* = 2.26×10^{-5}, *P*-value threshold = 1, Beta = 0.079, SE = 0.008, r^2 = 0.008, *P* = 2.26×10^{-5}).

Polygenic scores derived using household income in UK Biobank predicted a significant proportion of phenotypic variance for household income in GS: SFHS at each of the *P*-value thresholds used. The most predictive polygenic score was derived using a *P*-value threshold of 0.5 (*P*-value threshold = 0.01, Beta = 0.035, SE = 0.008, r^2 = 0.001, *P* = 1.47×10^{-5}, *P*-value threshold = 0.05, Beta = 0.042, SE = 0.008, r^2 = 0.002, *P* = 1.82×10^{-7}, *P*-value threshold = 0.1, Beta = 0.046, SE = 0.008, r^2 = 0.002, *P* = 6.77×10^{-9}, *P*-value threshold = 0.5, Beta = 0.052, SE = 0.008, r^2 = 0.003, *P* = 5.07×10^{-11}, *P*-value threshold = 1, Beta = 0.051, SE = 0.008, r^2 = 0.003, *P* = 1.20×10^{-10}).

Function of genes identified by clumping and MAGMA

AF4/FMR2 Family, Member 3 (*AFF3*) encodes a tissue-restricted nuclear transcriptional activator that is preferentially expressed in lymphoid tissue, previously associated with lymphoblastic leukaemia [S77], intellectual disability [S78], and rheumatoid arthritis [S79].

Carbohydrate Sulfotransferase 10 (*CHST10*) encodes a protein necessary for synthesising the neuronally expressed carbohydrate HNK1, which is involved in neurodevelopment and synaptic plasticity [S80].

LON Peptidase N-Terminal Domain And Ring Finger 2 (*LONRF2*) has been associate with coeliac disease [S81].

Neuromedin S (*NMS*) plays an important role in regulating circadian rhythms [S82].

Phosducin-Like 3 (PDCL3) is involved in the process of angiogenesis [S83].

KAT8 Regulatory NSL Complex Subunit 1 (*KANSL1*) is involved in chromatin modification and has previously been associated with intellectual disability [S84].

Macrophage Stimulating 1 (*MST1*) belongs to a family of kinases that are associated with a number of pathologies, including cancer, endothelial malformations and autoimmune disease [S85].

Expression levels of Ring Finger Protein 123 (RNF123) are associated with depression [S86].

Mutations in Microtubule-Associated Protein Tau (*MAPT*) have been associated with several neurodegenerative diseases, including Alzheimer's disease [S87].

Acylaminoacyl-Peptide Hydrolase (APEH) has an antioxidant function and has been associated with various cancers [S88].

Bassoon Presynaptic Cytomatrix Protein (*BSN*) encodes a scaffold protein expressed in the brain, is involved with neurotransmitter release and was previously associated with Crohn's disease [S89] and more recently with self-rated health [S90].

Pleckstrin Homology Domain Containing, Family M (With RUN Domain) Member 1 (*PLEKHM1*) encodes a protein essential for bone resorption and variants within the gene are associated with osteopetrosis [S91].

Sarcoglycan, Delta (35kDa Dystrophin-Associated Glycoprotein) (*SGCD*) encodes a subcomplex of the dystrophin-glycoprotein complex. Mutations in this gene have been associated with limb-girdle muscular dystrophy type 2F [S92] and cardiomyopathy [S93].

Dystroglycan 1 (Dystrophin-Associated Glycoprotein 1) (*DAG1*) encodes a laminin binding component of the dystrophin-glycoprotein complex. Mutations in *DAG1* are associated with a number of muscular dystrophies [S94].

Genetic variants in the Corticotropin Releasing Hormone Receptor 1 (*CRHR1*) have been associated with alcoholism [S95] and anxiety disorders [S96].

Aminomethyltransferase (*AMT*) encodes one of four critical components of the glycine cleavage system. Mutations in this gene have been associated with glycine encephalopathy [S97].

Zinc Finger, DHHC-Type Containing 11 (*ZDHHC11*) is located in a genomic region associated with lung [S98] and bladder cancers [S99].

1-Aminocyclopropane-1-Carboxylate Synthase Homolog (Arabidopsis)(Non-Functional)-Like (*ACCSL*)

KANSL1 MAPT, PLEKHM1 and *CRHR1* are in a region on chromosome 17 recently associated with Alzheimer's Disease [S100].

Comparison between income in the full data set and income in the restricted sample of 88,183

We first performed GCTA-GREML using the reduced sample size and found a very similar heritability estimate of 12% (SE = 0.7%). The results of the GWAS can be seen in Figure S3, shows the genome wide significant SNPs. The results of the GWAS on the reduced data set revealed 12 new genome-wide significant SNPs in 2 independent regions on chromosome 9. The SNP rs139128645, also on chromosome 9, did fall within an intron in the *EHMT1* gene. This gene has previously been associated with Kleefstra syndrome [S101] which includes symptoms such as developmental delay as well as learning difficulties. Another result of the loss of sample size was that the significant SNPs found using the whole sample were no longer significant at the genome-wide threshold of 5×10^{-8}. The results indicate that the beta weights and the standard errors of the genome-wide significant SNPs for both the reduced and full data sets were highly similar and that the fluctuation of sample size between these two comparisons is the most likely reason for the small difference in the *P*-values found between the full and reduced sample size, rather than any bias introduced from individuals residing together. This conclusion is also supported by the results of the gene based statistics, genetic correlations, partitioned heritability and the polygenic profile scores (as the genetic overlap between income and the health and anthropometric traits is very similar, along with the proportion of variance explained using the polygenic profile scores. These follow up results are available from the author. Additionally, as for the full sample, enrichment was found for SNPs in within 500bp of H3K9ac SNPs as well as those found in conserved regions, but not for SNPs within 500 bp of the DHS and conserved regions.

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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.

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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. Only stage 1 data were used for LD Score regression.

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