The effect of body-mass-index and type 2 diabetes on socioeconomic status: a two-sample multivariable Mendelian randomization study

Online Supplementary Material

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Online Supplementary material

Supplementary material 1: supplementary information on the modelling approach

Supplementary material 2: SNPs associated with BMI and type 2 diabetes.

Supplementary material 3: sensitivity analysis using other estimation methods (univariate MR)

Supplementary material 4: results from the phenoscanner search and sensitivity analysis

Supplementary material 1: supplementary information on the modelling approach

1.1 Instrumental variables (IV) assumptions

To interpret the resulting estimates as causal effects, three common assumptions of instrumental variable estimation must hold: (1) the instrument is associated with the exposure (relevance), (2) the instrument is independent across observations (exchangeability), and (3) the instrument influences the outcome exclusively via the exposure (exclusion restriction) (1).

We satisfied the first assumption is by restricting the set of instruments to genome-wide significant SNPs ($p<5x10e^{-8}$).

In contrast, the second and third assumption cannot be tested directly. Among others, violations of assumption 2 occur in case of population stratification, when different ethnic subgroups are present with different allele frequencies. We overcame this issue by focusing on homogeneous ancestry groups, namely focusing on individuals with European ancestry (2).

Violations of the third assumption occur in case of linkage disequilibrium between the included SNPs or in case of pleiotropy. Vertical pleiotropy is present when the same phenotype starts a cascade of events, ultimately influencing the outcome. This is not problematic but rather the very essence of how MR works. Instead, horizontal pleiotropy, i.e. the same SNP independently influences multiple phenotypes, leads to violations of the third assumption and to biased estimates (1).

Existing GWAS studies showed that BMI and type 2 diabetes share genetic mechanisms (3-5). Corresponding signals were discovered at the *FTO, TCF7L2* and *MC4R* genes (3), but recent studies have revealed many more (4, 5). This overlap could potentially bias estimates of univariate MR analyses by violating the third IV assumption. For this reason, multivariable MR techniques can be used to overcome this limitation (6).

1.2 Data

Gene-Outcome Association

For the associations between genetic variants (SNPs) and socioeconomic outcomes, we the results from the GWAS pipeline developed by the MRC-IEU (version 2, January 2019), including 464,708 individuals of European ancestry from the UK Biobank (7). The UK Biobank is a large cohort study including more than 500,000 individuals, surveyed between 2006-2010 (age range 40-69) and recruited in 22 study centers across the UK (8). At baseline, self-reported, physical and biological information of participants was collected, allowing subsequent genotyping of all individuals. Characteristics of the population and data representativity were described in detail by Fry et al. (8). The GWAS study was performed using linear or logistic regression, controlling for genotype array, sex and the first 10 principal components from the UK Biobank (7). Full details of genotyping and imputation, quality control and methods applied were described in Mitchell et al. (2019) (7).

Please refer to Table S.1 for a comprehensive description of the outcomes included in our study (household income and regional deprivation) (9).

Gene-Exposure Association

For the associations between genetic variants (SNPs) and BMI or type 2 diabetes, we utilized the results from two meta-analysis of GWAS studies (10, 11), selecting only men and women with European ancestry. One of the requirements of two-sample MR is that the estimates for the exposure and those of the outcome are based on non-overlapping data sources (1). To avoid this overlap, we selected the most recent available evidence on BMI and diabetes associated SNPs, which did not include participants from the UK Biobank. The Research Ethics Committee granted the UK Biobank ethical approval (REC ref. 11/NW/0382). All participants gave written informed consent.

With respect to BMI, we used the results of a meta-analysis from the GIANT consortium (10), including 322,154 individuals from 125 studies. We identified 69 relevant SNPs reaching GWAS significance ($p<5x10e^{-8}$), clumped at $r2<0.01$ within 10,000 kb using the 1000 G reference panel (Supplementary Material 2).

For type 2 diabetes, we used summary-level data from a meta-analysis of the DIAGRAM consortium (11), including 26,676 cases and 132,532 controls from 18 studies. We selected 42 GWAS significant SNPs following the same procedure as for BMI to obtain independent signals. Type 2 diabetes cases were defined using the 1999 WHO criteria of fasting plasma glucose ≥7.0 mmol/L or 2-h plasma glucose ≥11.1 mmol/L, by hospital records appraisal or by diabetes medication use (11) (Supplementary Material 2).

All studies contributing to the GIANT and DIAGRAM consortia meta-analyses received ethical approval from the respective review boards (10, 11).

Table S.1: definitions of socioeconomic outcomes.

	Definition	Sample size for analysis	Type	Distibution			UK Biobank data field	Link
Income	Average annual household income before tax	397,751	Categorical	<18,000 £	106,377	19%	738	http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=738
				18,000-30,999 £	126,732	22%		https://gwas.mrcieu.ac.uk/datasets/ukb-b-7408/
				31,000-51,999 £	130,063	23%		
				52,000-100,000 £	100,303	18%		
				>100,000 £	27,020	5%		
				Do not know	23,481	4%		
				Prefer not to answer	54,182	10%		
					568,158	100%		
Regional deprivation	Townsend deprivation index based on postcode upon joining the UK Biobank and preceding national census areas (Townsend, Phillimore & Beattie, 1988)	462,464	Continuous	Mean	-1.29		189	http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=189
				SD	3.10			https://gwas.mrcieu.ac.uk/datasets/ukb-b-10011/
				Min	-6.26			
				Max	11.00			
				N	501,882			

Notes: the distribution refers to the whole population included in the UK Biobank. The included studies focused on individuals with European ancestry, reason why the sample size differs. However, since we did not have access to raw data, we could not compute the accurate distribution for the included population. We report here the distribution in the whole UK Biobank population as an approximation.

1.3 Estimators and heterogeneity

Given the presence of several variants as potential instruments for the risk factors, we estimated the effects using the *inverse-variance weighted (IVW) method,* combining the single Wald ratio estimates using a fixed-effect meta-analysis model (12). The intercept is forced to zero, thereby assuming no horizontal pleiotropy and ignoring possible pleiotropic effects via other exposures.

However, violations of the these assumption might be present. For this reason, we used also other methods to produce consistent estimates of the causal effect. However, they rely on further underlying assumptions about the available IVs. First, we used (simple or weighted) *median based* estimates. These will be unbiased if more than half of the instruments are valid, including only those SNPs contributing to 50% of the statistical weight (13). Furthermore, we employed the *MR Egger* method. This approach allowed us to relax the assumption that estimates must run through the origin, estimating both a slope and an intercept of the effect. These effect estimates are consistent and unbiased if the InSIDE assumption holds (Instrument Strength Independent of Direct Effect) (14). We computed standard errors for this method using bootstrapping with 1000 replications. Finally, we used the *MR-Robust Adjusted Profile Score* (RAPS) method (15). This approach models the pleiotropic effects of genetic variants directly using a random-effects distribution where the pleiotropic effects are assumed to be normally distributed with zero mean and unknown variance.

To test the presence of heterogeneity, we computed Cochran´s Q statistic (16) and the related I^2 statistic (17). Furthermore, to test for horizontal pleiotropy, we implemented the MR Egger intercept test in the univariate setting. If the intercept is significantly different from zero, horizontal pleiotropy is likely to bias the effect estimates (14). Additional tests of horizontal pleiotropy and heterogeneity were carried out in form of extensive graphical analysis of the effect estimates.

1.4 Packages and implementation in statistical softwares

All analyses were performed using the package “TwoSampleMR” (Version 0.5.2) and the MR-base platform (18) in the statistical software R (R project for statistical computing). The phenoscanner search was performed using the R package “MendelianRandomization” (Version 0.4.2) (19).

Supplementary material 2: SNPs associated with BMI and type 2 diabetes (Locke et al., 2015 and Scott et al., 2017)

Table S.2: SNPs included in the study.

SNP	chromosome	position	nearest locus	exposure	effect allele	other allele	eaf	beta	se	p-val	sample size
rs10968576	9	28414339	LINGO 2	BMI	G	A	0.2917	0.0249	0.0033	6.60693E-14	322061
rs6477694	9	111932342	FRRS1L/EPB41L4B	BMI	T	C	0.6417	-0.0174	0.0031	2.67301E-08	322048
rs1928295	9	120378483		BMI	C	T	0.425	-0.0188	0.0031	7.91006E-10	321979
rs4740619	9	15634326	CCDC171	BMI	C	T	0.4667	-0.0179	0.0031	4.56405E-09	321887
rs10733682	9	129460914	LMX1B	BMI	G	A	0.575	-0.0174	0.0031	1.83E-08	320727
rs17405819	8	76806584	HNF4G	BMI	C	T	0.3667	-0.0224	0.0033	2.07014E-11	322085
rs2033732	8	85079709	RALYL	BMI	C	T	0.7583	0.0192	0.0035	4.889E-08	321406
rs1167827	7	75163169	HIP1	BMI	G	A	0.5417	0.0202	0.0033	6.33301E-10	306238
rs2245368	7	76608143	DTX2P1-UPK3BP1-PMS2P11/DTX2	BMI	T	C	0.7583	-0.0317	0.0057	3.18698E-08	205675
rs13191362	6	163033350	PRKN	BMI	G	A	0.2	-0.0277	0.0048	7.33905E-09	321902
rs2033529	6	40348653	TDRG1	BMI	G	A	0.2583	0.019	0.0033	1.388E-08	321917
rs9400239	6	108977663	FOXO3	BMI	C	T	0.7	0.0188	0.0033	1.61298E-08	321988
rs205262	6	34563164	ILRUN	BMI	G	A	0.2667	0.0221	0.0035	1.75299E-10	315542
rs2207139	6	50845490	RPS17P5	BMI	G	A	0.1	0.0447	0.004	4.12572E-29	322019
rs2112347	5	75015242	SLC25A5P9/POC5	BMI	G	T	0.375	-0.0261	0.0031	6.19156E-17	322019
rs13107325	4	103188709	SLC39A8	BMI	T	C	0.1167	0.0477	0.0068	1.82516E-12	321461
rs11727676	4	145659064	HHIP	BMI	C	T	0.075	-0.0358	0.0064	2.55E-08	296401
rs10938397	4	45182527	THAP12P9	BMI	G	A	0.4333	0.0402	0.0031	3.20479E-38	320955
rs17001654	4	77129568	SCARB2	BMI	G	C	0.1583	0.0306	0.0053	7.75997E-09	233722
rs2365389	3	61236462	FHIT	BMI	T	C	0.3417	-0.02	0.0031	1.629E-10	316768
rs3849570	3	81792112	GBE1	BMI	A	C	0.3667	0.0188	0.0034	2.601E-08	284339
rs13078960	3	85807590	CADM2	BMI	G	T	0.1833	0.0297	0.0039	1.737E-14	322135
rs16851483	3	141275436	RASA2	BMI	T	G	0.0917	0.0483	0.0077	3.54797E-10	233929
rs6804842	3	25106437		BMI	G	A	0.575	0.0185	0.0031	2.476E-09	321463
rs1516725	3	185824004	ETV5/DGKG	BMI	C	T	0.9083	0.0451	0.0046	1.88582E-22	320644
rs1528435	2	181550962		BMI	T	C	0.5833	0.0178	0.0031	1.196E-08	321924
rs7599312	2	213413231	ERBB4	BMI	A	G	0.2917	-0.022	0.0034	1.17301E-10	322024
rs10182181	2	25150296	DNAJC27/ADCY3	BMI	G	A	0.5	0.0307	0.0031	8.77607E-24	321759
rs13021737	2	632348	TMEM18	BMI	G	A	0.875	0.0601	0.004	1.11301E-50	318287
rs2121279	2	143043285	UBE2V1P14	BMI	T	C	0.1167	0.0245	0.0044	2.31302E-08	322065
rs12986742	2	58975143	LINC01122	BMI	C	T	0.5	0.0212	0.0037	1.006E-08	233833
rs1016287	2	59305625		BMI	C	T	0.675	-0.0229	0.0034	2.2532E-11	321969
rs29941	19	34309532	KCTD15	BMI	G	A	0.6667	0.0182	0.0033	2.40702E-08	321970
rs17724992	19	18454825	PGPEP1	BMI	G	A	0.3083	-0.0194	0.0035	3.41499E-08	319588

SNP	chromosome	position	nearest locus	exposure	effect allele	other allele	eaf	beta	se	p-val	sample size
rs2287019	19	46202172	QPCTL	BMI	T	C	0.15	-0.036	0.0042	4.58458E-18	300921
rs1808579	18	21104888	NPC1/RMC1	BMI	T	C	0.475	-0.0167	0.0031	4.16898E-08	322032
rs6567160	18	57829135	RNU4-17P	BMI	C	T	0.2833	0.0556	0.0036	3.93007E-53	321958
rs17066856	18	58049656		BMI	C	T	0.1333	-0.0395	0.0055	6.22444E-13	319773
rs12940622	17	78615571	RPTOR	BMI	A	G	0.4583	-0.0182	0.0031	2.49402E-09	322032
rs1000940	17	5283252	NUP88/RABEP1	BMI	G	A	0.225	0.0192	0.0034	1.28399E-08	321836
rs879620	16	4015729	ADCY9	BMI	T	C	0.5917	0.0244	0.004	1.06101E-09	233835
rs758747	16	3627358	NLRC3	BMI	T	C	0.2667	0.0225	0.0037	7.47309E-10	308688
rs9926784	16	19941968		BMI	C	T	0.2083	-0.0265	0.0042	1.84901E-10	316274
rs3888190	16	28889486	ATP2A1/SH2B1	BMI	A	C	0.3583	0.0309	0.0031	3.13979E-23	321930
rs4889606	16	31011183	STX1B	BMI	G	A	0.3583	-0.0183	0.0031	4.85702E-09	321887
rs16951275	15	68077168	MAP2K5	BMI	C	T	0.225	-0.0311	0.0037	1.91117E-17	322098
rs3736485	15	51748610	DMXL2	BMI	G	A	0.575	-0.0176	0.0031	7.41208E-09	321398
rs10132280	14	25928179	LINC02306	BMI	A	C	0.3333	-0.023	0.0034	1.14104E-11	321797
rs7141420	14	79899454	NRXN3	BMI	T	C	0.6167	0.0235	0.0031	1.22999E-14	321970
rs12429545	13	54102206		BMI	A	G	0.1	0.0334	0.0047	1.09396E-12	312934
rs9579083	13	28017270	MTIF3	BMI	C	G	0.2333	0.0295	0.0047	3.46099E-10	233807
rs11057405	12	122781897	CLIP1	BMI	A	G	0.0917	-0.0307	0.0055	2.01902E-08	314111
rs7138803	12	50247468	BCDIN3D	BMI	A	G	0.4417	0.0315	0.0031	8.15267E-24	322092
rs2176598	11	43864278	HSD17B12	BMI	C	T	0.8	-0.0198	0.0036	2.97098E-08	316848
rs4256980	11	8673939	TRIM66	BMI	G	C	0.725	0.0209	0.0031	2.90001E-11	320028
rs3817334	11	47650993	MTCH2	BMI	T	C	0.45	0.0262	0.0031	5.14517E-17	321959
rs12286929	11	115022404	CADM1	BMI	G	A	0.4333	0.0217	0.0031	1.31009E-12	321903
rs11030104	11	27684517	BDNF-AS/BDNF	BMI	G	A	0.2	-0.0414	0.0038	5.55648E-28	322103
rs7899106	10	87410904	GRID1	BMI	G	A	0.05	0.0395	0.0071	2.95999E-08	321770
rs17094222	10	102395440	HIF1AN/Metazoa_SRP	BMI	C	T	0.2083	0.0249	0.0038	5.94155E-11	321770
rs543874	1	177889480	SEC16B	BMI	G	A	0.2667	0.0482	0.0039	2.61818E-35	322008
rs11165643	1	96924097	EEF1A1P11/RN7SL831P	BMI	T	C	0.575	0.0218	0.0031	2.07014E-12	320730
rs17024393	1	110154688	GNAT2/GNAI3	BMI	C	T	0.04167	0.0658	0.0088	7.0291E-14	297874
rs3101336	1	72751185		BMI	C	T	0.6491	0.0334	0.0031	2.66073E-26	316872
rs2820292	1	201784287	NAV1/IPO9-AS1	BMI	C	A	0.5083	0.0195	0.0031	1.834E-10	321707
rs657452	1	49589847	AGBL4	BMI	G	A	0.5833	-0.0227	0.0031	5.48151E-13	313651
rs6656785	1	75005776	TNNI3K/FPGT-TNNI3K/LRRC53	BMI	G	A	0.3833	0.0217	0.0031	3.82913E-12	321410

SNP	chromosome	position	nearest locus	exposure	effect allele	other allele	eaf	beta	se	p-val	sample size
rs7903146	10	114758349	TCF7L2	BMI	T	C	0.25	-0.0234	0.0034	1.11199E-11	322130
rs7903146	10	114758349	TCF7L2	T2DM	T	C	0.2892	0.29	0.013	9.3E-108	158186
rs1558902	16	53803574	FTO	BMI	A	T	0.45	0.0818	0.0031	7.5162E-153	320073
rs1558902	16	53803574	FTO	T2DM	A	T	0.4155	0.13	0.012	4.7E-25	158182
rs10193447	2	60552476	BCL11A	T2DM	T	C	0.5979	0.071	0.012	0.000000013	158186
rs1061810	11	43877934	HSD17B12	T2DM	A	C	0.2785	0.08	0.014	5.3E-09	158185
rs10882098	10	94444793		T2DM	C	T	0.5583	0.13	0.012	1.4E-26	158186
rs10965250	9	22133284	CDKN2B-AS1	T2DM	G	A	0.8	0.14	0.016	2.7E-17	158183
rs11257655	10	12307894	RN7SL198P/CDC123	T2DM	T	C	0.275	0.08	0.015	0.00000004	158186
rs11616380	13	80705315	SPRY2	T2DM	G	T	0.7148	0.09	0.014	3.9E-11	158184
rs11708067	3	123065778	ADCY5	T2DM	A	G	0.7871	0.11	0.015	8.8E-13	152598
rs11712037	3	12344730	PPARG	T2DM	C	G	0.8746	0.13	0.019	8.6E-13	158185
rs11759026	6	126792095	CENPW	T2DM	G	A	0.2371	0.091	0.015	5.8E-10	158185
rs12555274	9	22136440		T2DM	C	G	0.285543	0.12	0.014	1.7E-16	158183
rs1635852	7	28189411	JAZF1	T2DM	T	C	0.5016	0.092	0.012	3E-14	158184
rs2023681	22	30599562	MTMR3/HORMAD2	T2DM	G	A	0.8878	0.12	0.021	3.9E-09	158183
rs2215383	7	15062983		T2DM	C	T	0.4667	0.069	0.012	0.000000014	158184
rs2237895	11	2857194	KCNQ1	T2DM	C	A	0.322883	0.097	0.013	1.7E-13	158185
rs2292626	10	124186714	PLEKHA1	T2DM	C	T	0.5038	0.085	0.012	1.8E-12	158186
rs28650790	5	55861464	C5orf67	T2DM	T	C	0.1917	0.1	0.016	7.4E-10	158186
rs2925979	16	81534790	CMIP	T2DM	T	C	0.2977	0.074	0.013	0.000000027	158182
rs2943649	2	227105691		T2DM	G	C	0.6083	0.073	0.013	6.6E-09	158186
rs340874	1	214159256	PROX1	T2DM	C	T	0.5502	0.068	0.012	0.000000034	158184
rs35352848	3	23455582	UBE2E2	T2DM	T	C	0.7771	0.083	0.015	0.000000015	158185
rs3802177	8	118185025	SLC30A8	T2DM	G	A	0.6774	0.11	0.013	1.7E-17	158185
rs3821943	4	6299940	WFS1	T2DM	T	C	0.5351	0.1	0.012	4.2E-16	158185
rs4238013	12	4376089	CCND2	T2DM	C	T	0.2001	0.099	0.017	3.6E-09	158183
rs429358	19	45411941	APOE	T2DM	T	C	0.8475	0.12	0.019	1.4E-10	152543
rs4402960	3	185511687	IGF2BP2	T2DM	T	G	0.3056	0.14	0.013	2.7E-25	152598
rs4774420	15	62117975	C2CD4A	T2DM	C	T	0.7024	0.075	0.013	0.000000027	158185
rs4846569	1	219771721	ZC3H11B	T2DM	C	T	0.7368	0.077	0.013	8.8E-09	158184
rs5219	11	17409572	KCNJ11	T2DM	T	C	0.3828	0.068	0.012	0.000000043	158185
rs56348580	12	121432117	HNF1A (TCF1)	T2DM	G	C	0.6831	0.073	0.013	0.000000025	158183

SNP	chromosome	position	nearest locus	exposure	effect allele	other allele	eaf	beta	se	p-val	sample size
rs62530366	8	145536056	HSF1	T2DM	G	A	0.322085	0.076	0.013	0.000000019	158185
rs6757251	2	43734847	THADA	T2DM	C	T	0.9011	0.13	0.021	1.9E-10	158186
rs7428936	3	64710850	ADAMTS9	T2DM	T	C	0.5905	0.07	0.012	0.00000001	158185
rs7451008	6	20673880	CDKAL1	T2DM	C	T	0.2606	0.17	0.013	3.8E-37	158185
rs756852	11	2663891	KCNQ1	T2DM	G	A	0.5975	0.09	0.014	3.6E-10	158185
rs757209	17	36102833	HNF1B (TCF2)	T2DM	G	A	0.578	0.083	0.014	1.1E-09	149849
rs76550717	11	72428172	ARAP1 (CENTD2)	T2DM	A	G	0.8299	0.096	0.016	3.8E-09	158185
rs8056814	16	75252327	BCAR1	T2DM	G	A	0.9168	0.15	0.023	3.7E-11	158182
rs810517	10	80942620	ZMIZ1	T2DM	C	T	0.5146	0.089	0.013	1.3E-12	152599
rs9410573	9	84311800	TLE1	T2DM	T	C	0.5986	0.073	0.013	0.00000002	158183
rs952471	15	77776498	HMG20A	T2DM	G	C	0.6869	0.082	0.013	4E-10	158185

Note: BMI body-mass-indes, T2DM type 2 diabetes mellitus, EAF effect allele frequency, SE standard error. Based two meta-analyses carried out by the GIANT consortium (Locke et al. 2015) and DIAGRAM consortium (Scott et al. 2017).

Supplementary material 3: sensitivity analysis using other estimation methods (univariate MR)

Table S.3: results of the univariate MR using different estimation methods.

	β	95% CI	pval	Q pval	I^2	intercept pval
HH income (SD)						
BMI						
IVW	-0.092	[-0.138; -0.047]	0	0	71%	
MR Egger	-0.045	[-0.11; 0.019]	0.08	0	71%	0.359
Simple median	-0.081	[-0.124; -0.038]	0.001			
Weighted median	-0.065	[-0.109; -0.022]	0.003			
RAPS	-0.085	[-0.128; -0.042]	0			
Type 2 diabetes						
IVW	-0.002	[-0.005; 0.008]	0.793	0	50%	
MR Egger	-0.005	[-0.014; 0.02]	0.312	0	49%	0.702
Simple median	-0.008	[-0.011; 0.009]	0.276			
Weighted median	-0.007	[-0.009; 0.012]	0.253			
RAPS	-0.002	[-0.006; 0.008]	0.774			
Deprivation (SD)						
BMI						
IVW	0.051	[0.022; 0.079]	0.001	0	57%	
MR Egger	0.013	[-0.036; 0.057]	0.282	0	55%	0.045
Simple median	0.042	[0.009; 0.076]	0.011			
Weighted median	0.029	[-0.002; 0.061]	0.066			
RAPS	0.045	[0.013; 0.077]	0.006			
Type 2 diabetes						
IVW	0.002	[-0.005; 0.008]	0.634	0.524	0%	
MR Egger	0.003	[-0.012; 0.019]	0.346	0.516	0%	0.375
Simple median	-0.001	[-0.011; 0.009]	0.848			
Weighted median	0.002	[-0.009; 0.012]	0.761			
RAPS	0.001	[-0.006; 0.008]	0.816			

Notes: β: marginal effect; CI: confidence interval; SD: standard deviation; HH income: household income; Q pval: p-value of the Cochrane´s Q statistic; IVW: inverse variance weighted estimator; MR: Mendelian randomization; RAPS: robust-adjusted profile score.

Supplementary material 4: results from the phenoscanner search and sensitivity analysis

To assess further potential violations of the exclusion restriction via horizontal pleiotropy, we looked for additional overlaps between the selected SNPs and other potential exposures using the phenoscanner (19). Four diabetes or BMI associated SNPs were also found to be significantly associated ($p<5x10e^{-8}$) with other illnesses (Chron´s disease, schizophrenia, systemic lupus erythematosus, Alzheimer´s disease and dementia) (Supplementary Material 3). Since the effect of these illnesses on the considered SES outcomes is not straightforward, we included these SNPs in the main analysis and excluded them in a sensitivity analysis.

Table S.4: results from the phenoscanner search.

SNP	allele 1	allele 2	trait	direction	study	year
rs13107325	T	C	Schizophrenia	+	Goes FS	2015
	T	C	Crohns disease	+	IBDGC	2015
rs1635852	C	T	Systemic lupus erythematosus and Systemic sclerosis	NA	Martin JE	2013
rs3888190	C	A	Crohns disease	NA	IBDGC	2012
	C	A	Crohns disease	-	IBDGC	2015
	C	A	Inflammatory bowel disease	-	IBDGC	2015
rs429358	C	T	Dementia with Lewy bodies	+	Guerreiro R	2018
	C	T	Late onset Alzheimers disease	NA	Hu X	2011
	C	T	Alzheimers disease	+	IGAP	2013
	C	T	Alzheimers disease age of onset	NA	Kamboh MI	2011
	C	T	Alzheimers disease biomarkers	NA	Ramanan VK	2013
	C	T	Cerebrospinal AB1 42 levels in Alzheimers disease dementia	NA	Ramirez A	2014

Note: associations retrieved using the phenoscanner in the R package "MendelianRandomization" (Version 0.4.2) (Yavorska & Burgess, 2017). Retrieved associations were restricted to other illnesses. NA not available.

Table S.4.1: univariate analysis excluding potentially pleiotropic SNPs

		HH income (SD)						Deprivation (SD)					
Exposure		**β**	**95% CI**	**pval**	**Q pval**	**I^2**	**intercept pval**	**β**	**95% CI**	**pval**	**Qpval**	**I^2**	**intercept pval**
BMI													
	IVW	-0.077	[-0.12 - -0.035]	0.000 ***	0.000	66%		0.053	[0.023 - 0.082]	0.000 ***	0.000	57%	
	MR Egger	-0.032	[-0.097 - 0.033]	0.165	0.000	65%	0.234	0.008	[-0.041 - 0.056]	0.399	0.000	55%	0.060
	Simple median	-0.070	[-0.114 - -0.026]	0.002 **				0.042	[0.008 - 0.076]	0.016 *			
	Weighted median	-0.065	[-0.106 - -0.024]	0.002 **				0.029	[-0.004 - 0.061]	0.081			
	RAPS	-0.075	[-0.113 - -0.036]	0.000 ***				0.047	[0.016 - 0.079]	0.003 **			
T2DM													
	IVW	0.000	[-0.012 - 0.012]	0.976	0.000	50%		0.001	[-0.006 - 0.007]	0.790	0.570	0%	
	MR Egger	-0.006	[-0.029 - 0.016]	0.293	0.000	51%	0.743	0.005	[-0.012 - 0.021]	0.286	0.558	0%	0.401
	Simple median	-0.007	[-0.021 - 0.007]	0.337				-0.001	[-0.011 - 0.009]	0.850			
	Weighted median	-0.006	[-0.019 - 0.008]	0.403				0.002	[-0.009 - 0.012]	0.768			
	RAPS	0.000	[-0.012 - 0.012]	0.994				0.000	[-0.007 - 0.007]	0.955			

Notes: β: marginal effect; CI: confidence interval; HH income: household income; BMI: body-mass-index; T2DM: type 2 diabetes;IVW: inverse variance weighted; MR: Mendelian randomization; RAPS: robust-adjusted profile score; Significance: ***p<0.05, **p<0.01, *p<0.001.

Table S.4.2: multivariate analysis excluding potentially pleiotropic SNPs

	HH income (SD)			Deprivation (SD)		
Exposure	**β**	**95% CI**	**pval**	**β**	**95% CI**	**pval**
BMI						
IVW	-0.076	[-0.115 - -0.037	0.000 ***	0.051	[0.024 - 0.077]	0.000 ***
MR Egger	-0.075	[-0.114 - -0.036]	0.000 ***	0.051	[0.025 - 0.078]	0.000 ***
T2DM						
IVW	0.000	[-0.014 - 0.014]	0.997	0.000	[-0.009 - 0.01]	0.956
MR Egger	0.000	[-0.014 - 0.014]	0.989	0.000	[-0.009 - 0.01]	0.968

Notes: β: marginal effect; CI: confidence interval; HH income: household income; BMI: body-mass-index; T2DM: type 2 diabetes;IVW: inverse variance weighted; MR: Mendelian randomization; RAPS: robust-adjusted profile score; Significance: ***p<0.05, **p<0.01, *p<0.001.

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