

Evaluating the causal associations between subjective wellbeing and cardiometabolic health: a Mendelian randomisation study

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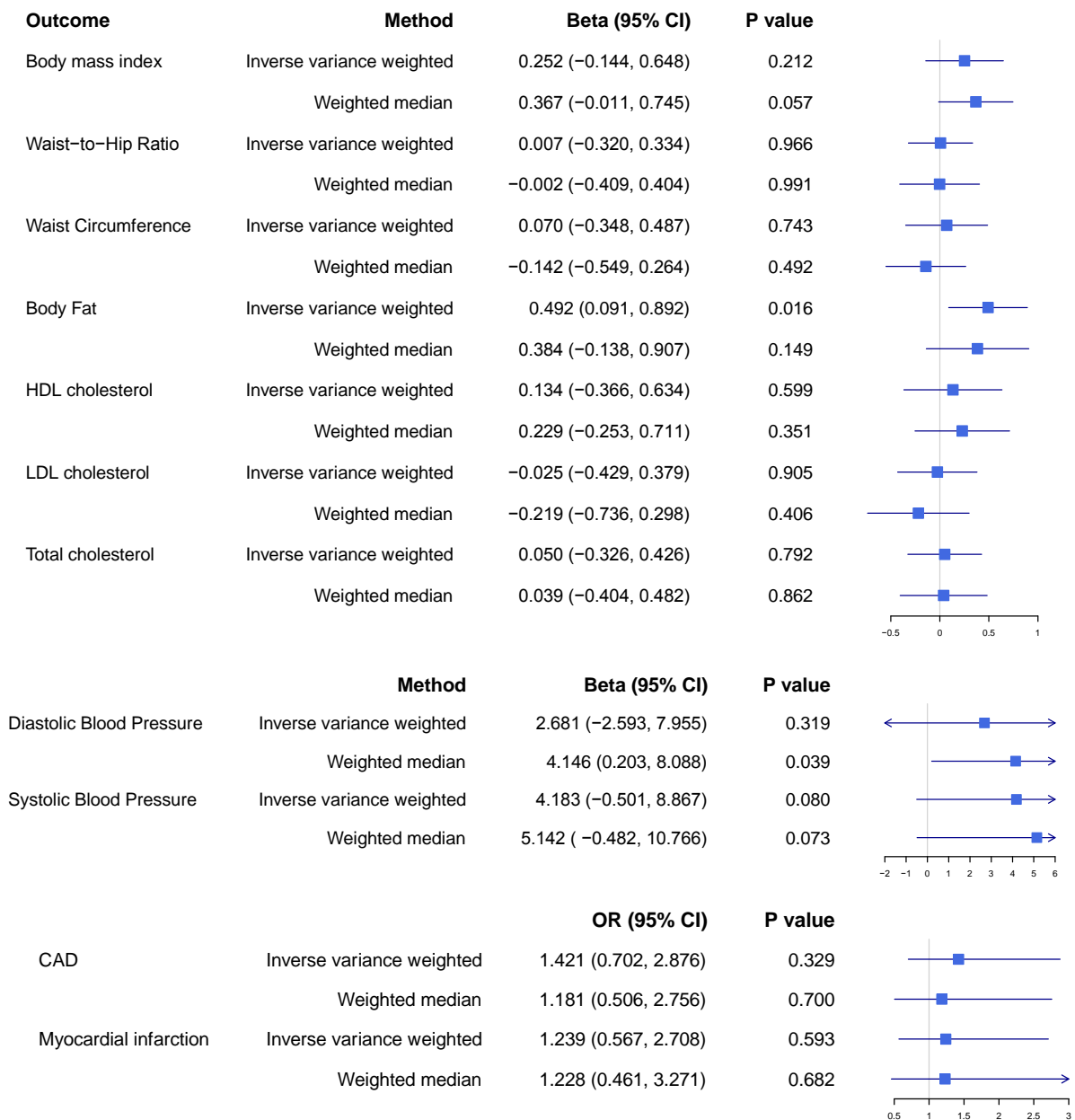
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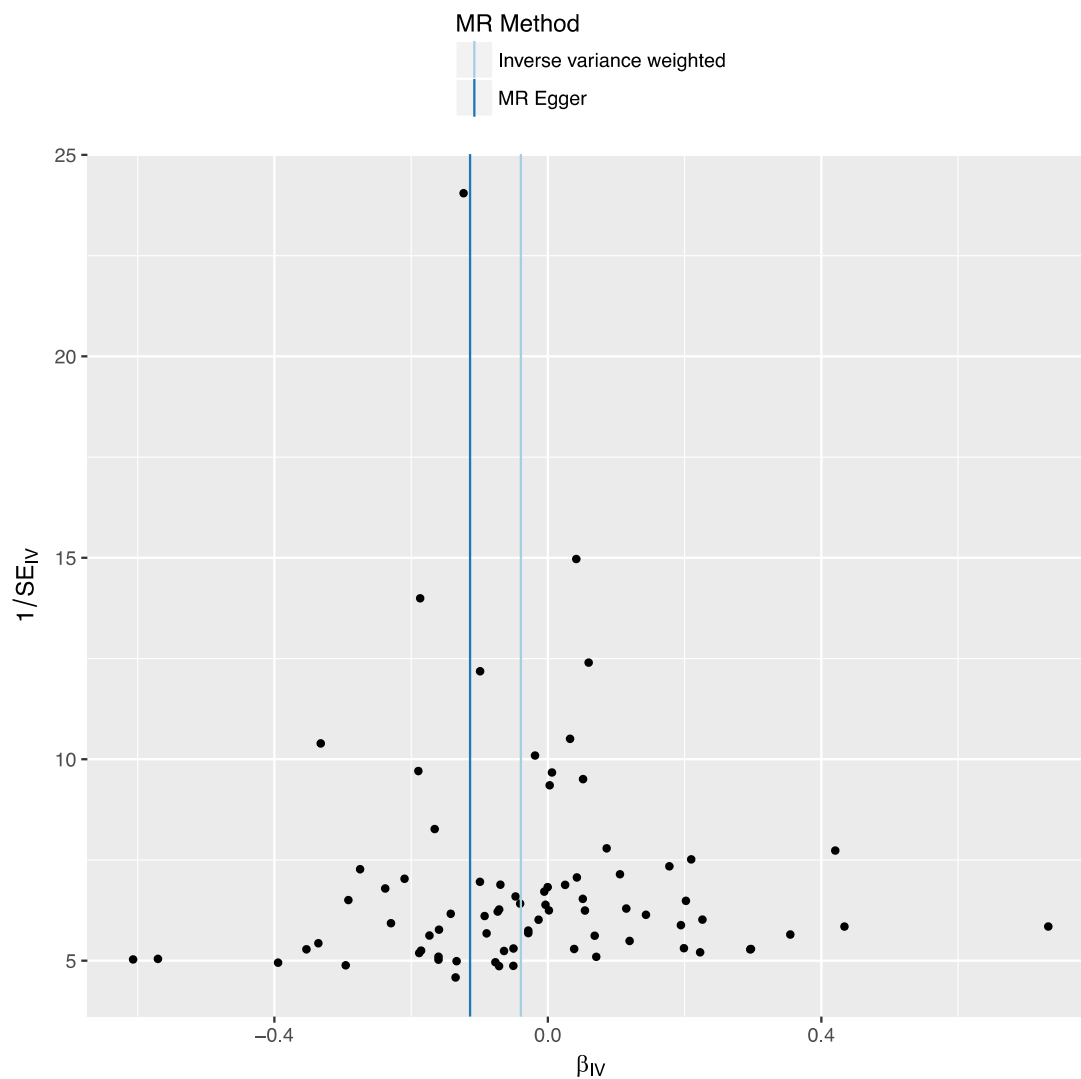
Figure S1. Two-sample MR analysis: the effect of subjective wellbeing on cardiometabolic health outcomes using 3 genome-wide significant variants as the instrument for subjective wellbeing.



The genetic instrument for the exposure, subjective wellbeing, was 3 genome-wide significant SNPs that each explain 0.1% of the variance, identified by the SSGAC [1]. Due to a restricted number of SNPs, MR-Egger, MBE and MR-PRESSO could not be conducted.

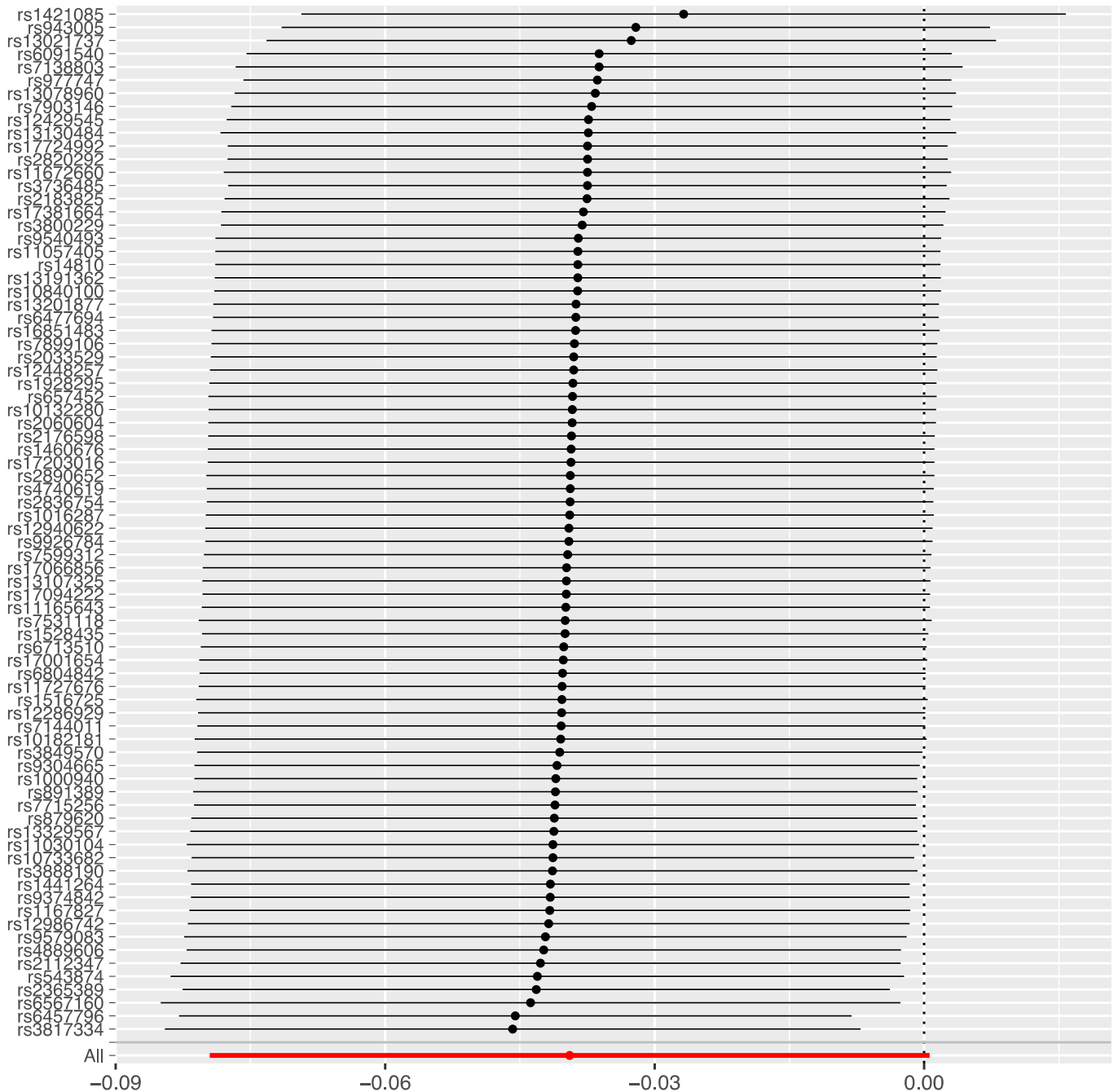
One unit increase of subjective wellbeing is equivalent to one standard deviation increase of the subjective wellbeing composite continuous scale. The genetic instrument was the 3 genome-wide significant SNPs for subjective wellbeing from Okbay et al [1]. Suitable proxies were identified at an LD cut-off $R^2 > 0.8$. Arrows on confidence intervals indicate they extend beyond the axis. Phenotype scores for all measures were standardised apart from for blood pressure which is represented on a different scale. There was no clear evidence to suggest a causal effect of subjective wellbeing on any of the health outcomes (see Figure 2).

Figure S2. Funnel plot of individual SNP effects of BMI on wellbeing.



MR Egger and IV weighted estimates are represented with blue lines. On the x-axis, β_{IV} represents the effect size of each SNP. On the y-axis, $1/SE_{IV}$ represents the inverse standard error for each SNP effect.

Figure S3. Leave-one-out analysis: each row represents a two-sample MR analysis of BMI on subjective wellbeing using all of the genome-wide significant SNPs available from Locke et al. [2] except for the SNP listed on the y-axis. The point represents the effect size with that SNP removed and the line represents the standard error.



Leave-one-out analysis was conducted using MR Base [3] to identify if any individual SNPs were driving the association between BMI and wellbeing. Results are shown in Figure S2. The SNP with the largest contribution to the effect is rs1421085 located on chromosome 16 in the second intron of the FTO (fat mass and obesity associated) gene. FTO has been repeatedly associated with obesity in different populations [4]. However, the biological consequences of intronic FTO SNPs are still unknown. They are currently thought to play a regulatory role in FTO gene expression in the hypothalamus [5].

Although research is not completely certain of the role of FTO, its large effect size and robust association with obesity suggest that this gene has the largest effect in the two-sample MR because of its BMI effect size rather than because of pleiotropic effects.

Figure S4. Bias plots of association with baseline confounders for BMI, comparing observational and MR analyses

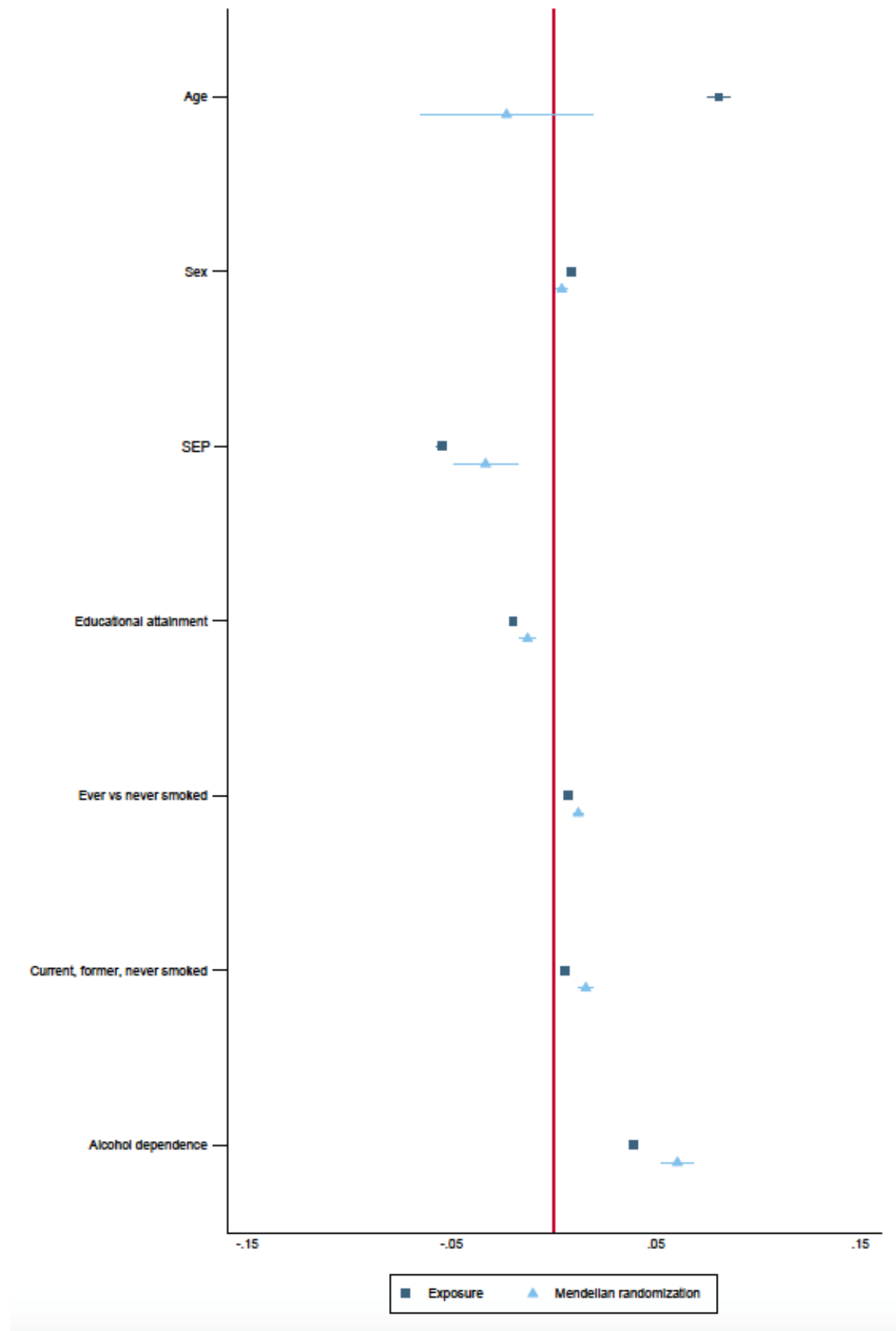


Table S1. Percentage sample overlap between the SSGAC GWAS for subjective wellbeing [1] and each of the GWAS for cardiometabolic health

Trait	GWAS Consortia			% Sample Overlap
Coronary Artery Disease	Nikpay [6]	2015	CARDIoGRAMplusC4D	6%
Total Cholesterol	Willer [7]	2013	GLGC	4%
HDL Cholesterol	Willer [7]	2013	GLGC	4%
LDL Cholesterol	Willer [7]	2013	GLGC	4%
Myocardial Infarction	Nikpay [6]	2015	CARDIoGRAMplusC4D	6%
Diastolic Blood Pressure	Wain [8]	2017	N/A	19%
Systolic Blood Pressure	Wain [8]	2017	N/A	19%
BMI	Locke [2]	2015	GIANT	36%
Waist to Hip Ratio	Shungin [9]	2015	GIANT	32%
Waist Circumference	Shungin [9]	2015	GIANT	32%
Body Fat	Lu [10]	2016	N/A	9%

Table S2. Descriptions of GWAS demographics

Phenotype	GWAS Phenotype Definition	Mean Age (years)	Covariates	Population Stratification	Instrument F statistic
Subjective Wellbeing	Any items of scales capturing positive affect or life satisfaction (e.g. “During the past week, I was happy?” and “How satisfied are you with your life as a whole?” respectively). The two were pooled and equally weighted.	-	sex, age, age ² and cohort specific covariates e.g. batch effects	At least 4 PCs	20.00
Coronary Artery Disease	Criteria for defining cases is given separately for each cohort in the cohort descriptions supplementary note [6]. Of the CAD cases, ~70% had a reported history of MI.	-	Given for each cohort in the cohort descriptions supplementary note [6].	Given for each cohort in the cohort descriptions supplementary note [6].	60.69
Myocardial Infarction		-			59.97
Total Cholesterol	Where possible, individuals on lipid lowering medication were excluded.	-	Sex, age, age ²	24% of cohorts controlled for population structure using either PC or	138.38
HDL Cholesterol	The majority of studies measured lipids after >8 hours of fasting.	-		mixed model approaches	119.75
LDL Cholesterol	24% of studies directly measured cholesterol and the rest estimated it using the Friedewald formula. Total cholesterol is calculated from HDL, LDL and triglycerides.	-			159.76
Diastolic Blood Pressure	Diastolic blood pressure measured in mmHg. 10mmHg was added to their score if they were known to be taking antihypertensive medication. Specific conditions differed for each cohort, details can be found in Supplementary materials of [8].	53.13	sex, age, age ² , BMI	Each cohort adjusted as necessary	48.59

Systolic Blood Pressure	Systolic blood pressure measured in mmHg. 15mmHg was added to their score if they were known to be taking antihypertensive medication. Specific conditions differed for each cohort, details can be found in Supplementary materials of [8].	53.13	sex, age, age ² , BMI	Each cohort adjusted as necessary	49.22
BMI	Combination of measured or self-reported BMI. Weight in kg per height in m ² .	56.39	Sex, age, age ² , BMI and cohort-specific covariates if necessary	Each cohort adjusted as necessary	66.83
Waist to Hip Ratio	The ratio of waist circumference to hip circumference adjusted for BMI.	54.39	Sex, age, age ² , BMI and cohort-specific covariates if necessary	Each cohort adjusted as necessary	54.07
Waist Circumference	Waist circumference adjusted for BMI.	54.39	Sex, age, age ² , BMI and cohort-specific covariates if necessary	Each cohort adjusted as necessary	59.85
Body Fat %	Body fat percentage was measured using either bioimpedance analysis or dual energy X-ray absorptiometry (DEXA).	-	Sex, age, age ² and study-specific covariates	Each cohort adjusted as necessary	44.53

Note. For further description of all phenotypes see individual papers supplementary materials. Mean F statistic of greater than 10% indicates a suitable instrument [11].

Table S3. Linear regression of the three genome-wide significant SNPs for subjective wellbeing predicting happiness in the UK Biobank independent sample (N= 242,219).

	Effect allele	Beta (95% CI)	p-value
rs2075677	G	-0.013 (-0.021, -0.005)	0.001
rs4958581	C	-0.001 (-0.009, 0.007)	0.814
rs3756290	A	-0.002 (-0.010, 0.006)	0.657

Note. The first release of genetic data from the UK Biobank (~150,000) was part of the SSGAC discovery GWAS [1] therefore genetic data from the second release (~350,000) was used in this independent analysis.

Table S4. Overlap between SNPs associated with subjective wellbeing at $p < 5 \times 10^{-5}$ and their association with Major Depressive Disorder

SNP	CHR	BP	A1	A2	EAF	Subjective Wellbeing			Major Depressive Disorder		
						Beta	SE	P-value	OR	SE	P-value
rs10172421	2	204238402	A	C	0.105	-0.021	0.005	1.11E-05	1.002	0.012	0.867
rs1028144	2	99279354	A	G	0.530	0.013	0.003	3.97E-05	0.989	0.008	0.160
rs1030443	20	17408386	C	G	0.856	-0.019	0.005	3.33E-05	1.024	0.011	0.035
rs1075737	7	103071193	A	G	0.185	-0.019	0.004	8.11E-06	1.024	0.011	0.026
rs10769190	11	46151490	T	C	0.198	0.018	0.004	2.19E-06	0.991	0.010	0.361
rs10895581	11	104002184	T	C	0.797	0.016	0.004	3.25E-05	0.987	0.010	0.170
rs10923025	1	88579746	T	G	0.946	-0.029	0.007	3.05E-05	0.990	0.018	0.573
rs11043207	12	122268696	C	G	0.797	0.018	0.004	3.84E-05	0.997	0.011	0.812
rs11073619	15	85188839	T	C	0.105	0.025	0.005	3.42E-06	1.024	0.013	0.074
rs1135436	10	63956232	A	T	0.147	-0.020	0.005	1.66E-05	0.979	0.011	0.062
rs11612312	12	52349088	T	C	0.806	0.019	0.004	1.37E-06	0.958	0.010	1.41E-05
rs11644362	16	12994097	T	C	0.459	0.014	0.003	2.06E-05	0.989	0.008	0.163
rs11668122	19	57516240	A	G	0.920	0.028	0.007	3.38E-05	1.013	0.015	0.374
rs11691770	2	168633442	T	G	0.039	0.037	0.008	8.52E-06	0.992	0.020	0.680
rs11751387	6	124633499	T	C	0.097	0.021	0.005	3.07E-05	1.019	0.013	0.133
rs12062152	1	234267329	A	G	0.039	0.035	0.008	2.10E-05	0.992	0.019	0.662
rs12143280	1	211547522	T	C	0.944	0.038	0.008	6.46E-07	1.002	0.017	0.888
rs12147610	14	55190709	T	C	0.306	-0.019	0.005	4.67E-05	1.005	0.011	0.653
rs12152057	21	25056215	A	C	0.674	0.015	0.003	1.14E-05	1.001	0.009	0.940
rs12298541	12	66306441	A	C	0.356	0.016	0.003	2.28E-06	0.999	0.008	0.893
rs12460988	19	31162121	T	C	0.573	-0.014	0.003	1.67E-05	0.991	0.008	0.281
rs12474324	2	19346130	A	G	0.942	0.027	0.006	1.18E-05	1.002	0.015	0.902
rs12995715	2	63676678	C	G	0.239	-0.016	0.004	1.46E-05	1.007	0.009	0.451
rs13235506	7	53785701	T	G	0.955	-0.034	0.007	1.96E-06	1.038	0.020	0.059
rs1328835	13	109883183	C	G	0.944	0.027	0.007	3.20E-05	0.979	0.016	0.184

rs13387164	2	154144551	A	G	0.091	-0.023	0.005	5.98E-06	1.013	0.013	0.339
rs1361360	10	20795797	T	C	0.401	0.014	0.003	3.30E-05	0.996	0.008	0.654
rs1462450	18	49204707	A	G	0.892	0.020	0.005	1.11E-05	0.987	0.012	0.253
rs1520724	12	94865477	T	C	0.586	0.013	0.003	4.65E-05	0.995	0.008	0.496
rs1556477	9	20735284	A	G	0.634	0.014	0.003	3.42E-05	1.000	0.008	0.975
rs16847494	3	137532063	C	G	0.754	0.015	0.004	3.38E-05	0.989	0.009	0.215
rs17005492	4	140960772	T	C	0.785	0.018	0.004	2.01E-06	0.990	0.010	0.270
rs17331012	4	12144655	A	G	0.129	-0.023	0.005	1.10E-06	1.002	0.012	0.864
rs17693963	6	27710165	A	C	0.897	-0.026	0.005	9.25E-07	1.071	0.013	1.24E-07
rs17766081	4	68064345	C	G	0.558	0.013	0.003	4.79E-05	0.992	0.009	0.395
rs2017279	10	3534725	A	G	0.679	0.016	0.003	3.15E-06	0.985	0.009	0.080
rs2058382	7	69579024	A	G	0.590	-0.015	0.003	6.12E-06	1.007	0.008	0.365
rs2075677	20	47701024	A	G	0.774	0.021	0.004	1.88E-08	0.991	0.009	0.328
rs210896	6	11729440	T	G	0.765	0.017	0.004	1.01E-05	1.000	0.010	0.993
rs2127737	16	73639443	T	C	0.843	0.018	0.004	2.08E-05	0.991	0.011	0.374
rs2212682	21	21527469	T	G	0.847	-0.019	0.005	3.94E-05	0.997	0.012	0.797
rs2321300	2	134582082	A	G	0.146	-0.017	0.004	3.41E-05	0.995	0.010	0.645
rs2409722	8	11039816	T	G	0.463	0.013	0.003	2.06E-05	1.004	0.008	0.591
rs258677	7	81733428	T	G	0.375	0.017	0.003	9.46E-08	0.997	0.008	0.747
rs2597455	4	163307671	T	G	0.623	-0.014	0.003	1.78E-05	1.006	0.008	0.482
rs281288	15	47681703	T	G	0.345	-0.016	0.004	1.99E-05	1.041	0.010	3.26E-05
rs2819873	10	81906119	T	C	0.052	0.030	0.007	1.32E-05	0.996	0.017	0.805
rs2911244	16	89521860	A	G	0.478	0.013	0.003	4.29E-05	0.990	0.008	0.221
rs3104708	16	10071193	A	G	0.118	-0.021	0.005	8.58E-06	0.996	0.012	0.723
rs35238	5	52293721	A	G	0.039	-0.040	0.010	4.75E-05	1.013	0.024	0.577
rs37241	5	89853342	C	G	0.058	0.036	0.009	4.73E-05	0.974	0.018	0.146
rs3756290	5	130951750	A	G	0.237	-0.016	0.004	1.44E-05	1.008	0.010	0.467
rs3828653	5	114482595	C	G	0.970	0.035	0.009	4.76E-05	1.028	0.021	0.184

rs4570163	8	123451096	T	C	0.702	-0.014	0.003	1.54E-05	1.006	0.008	0.510
rs4589952	3	95702105	T	C	0.155	-0.021	0.004	1.55E-06	1.017	0.011	0.131
rs4762896	12	22401911	T	C	0.265	-0.016	0.004	3.51E-05	1.001	0.010	0.950
rs4792196	17	11820388	A	T	0.188	0.018	0.004	4.18E-05	0.992	0.011	0.481
rs4810682	20	46387986	A	G	0.821	-0.021	0.005	3.61E-05	0.994	0.011	0.598
rs4842283	12	80822975	A	C	0.903	-0.029	0.006	1.94E-07	1.001	0.015	0.955
rs6073597	20	43629512	T	C	0.552	0.014	0.003	7.96E-06	0.992	0.008	0.289
rs6089930	20	61359001	A	G	0.457	-0.014	0.003	1.32E-05	0.999	0.008	0.938
rs6587766	1	57708088	T	C	0.041	0.047	0.009	2.52E-07	0.983	0.024	0.481
rs6598440	15	101795040	A	G	0.968	0.032	0.008	2.68E-05	1.040	0.019	0.039
rs6704609	2	122950483	C	G	0.955	0.028	0.007	3.65E-05	0.969	0.018	0.083
rs6772840	3	43854320	A	T	0.090	0.025	0.006	5.83E-06	0.988	0.015	0.392
rs6813656	4	82380368	T	C	0.968	-0.045	0.010	7.74E-06	0.991	0.022	0.682
rs7072297	10	44462360	C	G	0.843	0.018	0.004	3.55E-05	0.988	0.011	0.268
rs7149000	14	41897318	A	G	0.459	-0.014	0.003	4.77E-06	1.026	0.008	0.002
rs7239776	18	52578599	A	T	0.530	-0.016	0.003	3.31E-07	1.016	0.008	0.056
rs7445606	5	152200109	A	C	0.381	-0.013	0.003	4.86E-05	1.013	0.008	0.114
rs7487682	12	48579665	T	G	0.410	-0.013	0.003	3.43E-05	1.008	0.008	0.354
rs7584895	2	29229016	T	C	0.519	-0.014	0.003	1.15E-05	1.009	0.008	0.258
rs7939430	11	134631823	A	G	0.149	-0.019	0.004	3.40E-05	1.012	0.011	0.278
rs7952069	11	12917033	T	C	0.890	0.021	0.005	5.66E-06	1.000	0.013	0.977
rs8073904	17	79095144	A	G	0.855	-0.021	0.005	1.24E-05	1.009	0.013	0.495
rs8180800	7	4161793	T	C	0.388	0.013	0.003	4.97E-05	0.991	0.008	0.331
rs903834	11	10814116	A	G	0.407	0.015	0.003	1.17E-05	0.987	0.008	0.115
rs905456	3	30746255	A	G	0.429	-0.014	0.003	1.48E-05	1.005	0.008	0.525
rs9291932	5	68043243	T	C	0.718	0.015	0.004	4.28E-05	1.002	0.009	0.866
rs929814	19	30340412	A	G	0.638	0.013	0.003	3.33E-05	1.006	0.008	0.465
rs9528554	13	63282834	T	C	0.784	0.016	0.004	9.59E-06	1.013	0.009	0.155

rs976337	11	95011645	T	C	0.597	0.014	0.003	5.27E-06	0.996	0.008	0.654
rs9840016	3	159899731	T	C	0.778	-0.017	0.004	1.68E-05	0.985	0.010	0.114
rs9956636	18	31304974	T	C	0.377	-0.013	0.003	4.59E-05	1.023	0.008	0.005

Note. SNPs for subjective wellbeing are from Okbay [1] and have been extracted from the most recent GWAS of Major Depressive Disorder (MDD) [12]. None is associated with MDD in the current GWAS at the genome-wide level of significance. A1 = effect allele, A2 = non-effect allele, EAF = effect allele frequency. rG between subjective wellbeing and MDD was -0.65 (SE = 0.04) [12].

Table S5. Power calculation for two-sample Mendelian randomisation

Exposure	Variance Explained by the Instrument (r²)	Causal effect we have 80% power to detect
Wellbeing	0.01%	0.971 to 0.481
	0.05%	0.435 to 0.215
	0.5%	0.138 to 0.068
	1%	0.097 to 0.049
BMI	2.7% [2]	0.031
Waist-to-Hip ratio	1.4% [3]	0.044
Body Fat	0.58% [4]	0.068
HDL Cholesterol	1.6% [5]	0.041
LDL Cholesterol	2.4% [5]	0.033
Total Cholesterol	2.6% [5]	0.032
Waist circumference, diastolic blood pressure, systolic blood pressure, CAD, MI	0.05%	0.230
	0.5%	0.073
	1%	0.052
	2%	0.037

Note. Power calculations were conducted using Burgess' online calculator [1]. Causal effect refers to the change in outcome in SD units per SD change in exposure. Where possible, variance explained from the original GWAS paper was used. For waist circumference, blood pressure, CAD and MI r² was not reported so we give a range of values. For subjective wellbeing, variance explained at $p < 5 \times 10^{-5}$ was unknown, therefore a range of values are given. For all calculations we used the outcome sample size. For subjective wellbeing we present the range of values we can detect given the smallest sample size (83198 for LDL cholesterol) and the largest (339224 for BMI). All others had subjective wellbeing as the outcome so sample size is 298420.

Table S6. SNPs associated with BMI at the genome-wide level of significance

SNP Name	Effect Allele	Non-effect Allele	MAF	Beta	SE	p-value
rs1000940	G	A	0.225	0.018	0.003	1.81E-08
rs10132280	A	C	0.333	-0.022	0.003	1.40E-11
rs1016287	T	C	0.325	0.023	0.003	4.36E-12
rs10182181	A	G	0.500	-0.031	0.003	8.07E-26
rs10733682	A	G	0.425	0.019	0.003	2.46E-10
rs10938397	A	G	0.567	-0.040	0.003	1.42E-40
rs10968576	G	A	0.292	0.025	0.003	2.34E-14
rs11030104	A	G	0.800	0.042	0.004	6.66E-30
rs11057405	A	G	0.092	-0.030	0.005	1.22E-08
rs11126666	G	A	0.692	-0.020	0.003	1.32E-09
rs11165643	C	T	0.425	-0.022	0.003	1.43E-13
rs11191560	T	C	0.942	-0.031	0.005	2.08E-09
rs11583200	C	T	0.375	0.017	0.003	6.00E-09
rs1167827	A	G	0.458	-0.020	0.003	1.98E-10
rs11688816	A	G	0.542	-0.015	0.003	3.80E-07
rs11727676	C	T	0.075	-0.037	0.006	6.25E-09
rs11847697	T	C	0.042	0.037	0.007	2.61E-07
rs9581854	C	T	0.767	-0.030	0.005	9.28E-11
rs12286929	G	A	0.433	0.021	0.003	5.44E-13
rs12401738	A	G	0.425	0.020	0.003	2.04E-10
rs12429545	G	A	0.900	-0.032	0.004	3.15E-13
rs12446632	A	G	0.133	-0.040	0.004	1.81E-19
rs12566985	G	A	0.425	0.024	0.003	1.95E-15
rs12885454	C	A	0.633	0.020	0.003	9.09E-11
rs12940622	A	G	0.458	-0.018	0.003	3.64E-10
rs13021737	A	G	0.125	-0.060	0.004	5.44E-54
rs13078960	T	G	0.817	-0.029	0.004	1.42E-14
rs13107325	C	T	0.883	-0.047	0.007	1.06E-12
rs13191362	A	G	0.800	0.029	0.005	1.09E-09
rs13201877	A	G	0.917	-0.024	0.004	4.29E-08
rs1441264	A	G	0.550	0.017	0.003	2.96E-08
rs1460676	T	C	0.783	-0.021	0.004	4.98E-08
rs1516725	T	C	0.092	-0.045	0.004	1.39E-24
rs1528435	T	C	0.583	0.018	0.003	4.77E-09
rs1558902	A	T	0.450	0.081	0.003	1.13E-156
rs16851483	G	T	0.908	-0.048	0.008	1.85E-10
rs16907751	C	T	0.958	0.033	0.006	2.13E-07
rs16951275	C	T	0.225	-0.030	0.004	2.04E-18
rs17001654	C	G	0.842	-0.030	0.005	5.03E-09
rs17024393	C	T	0.042	0.061	0.008	1.64E-13
rs17094222	C	T	0.208	0.025	0.004	2.19E-11
rs17203016	G	A	0.200	0.021	0.004	3.41E-08
rs17405819	C	T	0.367	-0.022	0.003	1.17E-11
rs17724992	A	G	0.692	0.020	0.003	7.79E-09
rs1808579	T	C	0.475	-0.016	0.003	4.25E-08

rs1928295	C	T	0.425	-0.018	0.003	4.32E-10
rs2033529	G	A	0.289	0.018	0.003	1.39E-08
rs2033732	C	T	0.758	0.018	0.003	2.26E-07
rs205262	A	G	0.733	-0.021	0.003	2.70E-10
rs2075650	A	G	0.858	0.026	0.004	3.21E-09
rs2080454	A	C	0.608	-0.017	0.003	8.60E-09
rs2112347	G	T	0.375	-0.025	0.003	1.96E-17
rs2121279	T	C	0.117	0.024	0.004	1.92E-08
rs2176040	G	A	0.392	-0.015	0.003	1.33E-06
rs2176598	T	C	0.608	-0.015	0.003	3.47E-08
rs2207139	G	A	0.200	0.019	0.003	8.06E-31
rs2245368	T	C	0.100	0.045	0.004	7.01E-08
rs2287019	C	T	0.758	-0.029	0.005	1.68E-18
rs2365389	C	T	0.850	0.035	0.004	1.35E-10
rs2650492	A	G	0.658	0.020	0.003	1.29E-09
rs2820292	A	C	0.308	0.021	0.003	5.45E-10
rs2836754	C	T	0.492	-0.018	0.003	1.61E-08
rs29941	A	G	0.650	0.017	0.003	2.20E-08
rs3101336	T	C	0.333	-0.018	0.003	6.49E-26
rs3736485	A	G	0.351	-0.032	0.003	4.52E-08
rs3810291	A	G	0.425	0.016	0.003	6.35E-16
rs3817334	C	T	0.625	0.029	0.004	1.17E-17
rs3849570	A	C	0.550	-0.026	0.003	1.93E-08
rs3888190	A	C	0.367	0.018	0.003	3.45E-25
rs4256980	G	C	0.358	0.031	0.003	8.35E-12
rs4740619	T	C	0.725	0.021	0.003	6.36E-09
rs4787491	A	G	0.533	0.017	0.003	2.34E-06
rs492400	T	C	0.386	-0.015	0.003	4.87E-07
rs543874	G	A	0.675	-0.015	0.003	2.29E-40
rs6091540	C	T	0.267	0.050	0.004	2.14E-08
rs6465468	G	T	0.725	0.019	0.003	2.44E-06
rs6477694	C	T	0.675	-0.016	0.003	1.71E-08
rs6567160	C	T	0.358	0.017	0.003	6.68E-59
rs657452	A	G	0.283	0.056	0.004	2.12E-13
rs6804842	A	G	0.417	0.023	0.003	8.02E-10
rs7138803	G	A	0.425	-0.018	0.003	5.12E-26
rs7141420	T	C	0.558	-0.032	0.003	8.66E-15
rs7164727	T	C	0.617	0.023	0.003	3.92E-09
rs7239883	G	A	0.775	0.019	0.003	3.14E-07
rs7243357	G	T	0.317	0.015	0.003	9.14E-09
rs758747	C	T	0.133	-0.022	0.004	1.51E-10
rs7599312	G	A	0.733	-0.023	0.004	4.73E-11
rs7715256	G	T	0.708	0.021	0.003	8.85E-09
rs7899106	A	G	0.450	0.017	0.003	1.27E-08
rs7903146	T	C	0.950	-0.038	0.007	1.10E-12
rs9374842	T	C	0.250	-0.024	0.003	7.20E-09
rs9400239	C	T	0.742	0.020	0.003	6.77E-08
rs9540493	G	A	0.700	0.017	0.003	3.95E-09
rs9641123	G	C	0.550	-0.018	0.003	1.83E-07

rs977747	T	G	0.608	-0.019	0.004	2.18E-08
rs9914578	G	C	0.467	0.017	0.003	2.07E-08
rs9925964	G	A	0.167	0.020	0.004	9.35E-11

List of SNPs associated with BMI [1] used for one-sample Mendelian Randomisation.

Table S7. Regression dilution I^2 statistic for the heterogeneity of SNP-exposure effects.

Exposure	I^2
Subjective wellbeing	0.367
BMI	0.913
Body Fat	0.565
Waist-to-Hip Ratio	0.575
Waist Circumference	0.882
CAD	0.905
MI	0.903
LDL Cholesterol	0.986
HDL Cholesterol	0.971
Total Cholesterol	0.978
Diastolic Blood Pressure	0.774
Systolic Blood Pressure	0.689

Note: I^2 is a measure of the regression dilution of all SNP-exposure effects.

Regression dilution bias occurs when the SNPs are weakly associated with the exposure. This is also known as the 'NO Measurement Error' (NOME) assumption. The I^2 statistic for the SNP-exposure (GX) effects is a measure of NOME violation. In order to conduct MR Egger regression I^2 should be greater than 0.9 or else simulation extrapolation (SIMEX) correction should be applied [13].

Table S8. Tests of heterogeneity for physical health traits as the exposure and subjective wellbeing as the outcome.

Exposure	Method	Q	df	P-value
BMI	MR Egger	33.96	23	0.066
	Inverse-Variance Weighted	34.24	24	0.081
Waist-to-hip Ratio	MR Egger	35.12	34	0.415
	Inverse-Variance Weighted	36.03	35	0.420
Waist circumference	MR Egger	85.08	38	<0.001
	Inverse-Variance Weighted	90.64	39	<0.001
Body Fat	MR Egger	11.88	7	0.105
	Inverse-Variance Weighted	13.05	8	0.110
HDL cholesterol	MR Egger	76.9	65	0.148
	Inverse-Variance Weighted	78.4	65	0.141
LDL cholesterol	MR Egger	111.3	82	0.017
	Inverse-Variance Weighted	110.1	83	0.025
Total cholesterol	MR Egger	102.3	76	0.024
	Inverse-Variance Weighted	101	77	0.034
CAD	MR Egger	145	76	0.000
	Inverse-Variance Weighted	149.4	77	0.000
Myocardial infarction	MR Egger	29.95	13	0.005
	Inverse-Variance Weighted	27.81	14	0.015
Diastolic blood pressure	MR Egger	59.52	41	0.031
	Inverse-Variance Weighted	61.04	42	0.029
Systolic blood pressure	MR Egger	47.08	34	0.067
	Inverse-Variance Weighted	47.88	35	0.072

Note: df = degrees of freedom where degrees of freedom is equal to the number of SNPs -1. Q = Cochran's Q, a test of heterogeneity or dispersion in the SNP effects. Separate clusters of SNP effects suggest that they are acting through different pathways. This is an indicator that there might be a pleiotropic pathway.

Table S9. Tests of directional pleiotropic effects of the genetic instruments for physical health on subjective wellbeing.

Exposure	Intercept (95% CI)	P-value	MR-PRESSO Global Test	P-value
BMI	0.002 (-0.0001, 0.005)	0.070	157.36	<0.001
Waist-to-hip ratio	-0.003 (-0.008, 0.003)	0.353	38.74	0.387
Waist circumference	0.005 (-0.001, 0.010)	0.123	95.59	<0.001
Body fat	0.008 (-0.012, 0.028)	0.434	16.70	0.105
HDL cholesterol	-0.0003 (-0.002, 0.001)	0.769	115.17	0.019
LDL cholesterol	-0.001 (-0.003, 0.0003)	0.127	82.80	0.155
Total cholesterol	-0.0004 (-0.002, 0.002)	0.690	105.93	0.035
CAD	0.001 (-0.002, 0.003)	0.685	49.17	0.033
Myocardial infarction	-0.0001 (-0.006, 0.006)	0.994	42.49	0.002
Diastolic blood pressure	-0.002 (-0.006, 0.002)	0.312	63.93	0.029
Systolic blood pressure	-0.002 (-0.007, 0.003)	0.452	50.38	0.074

Note: Reported intercepts are the MR Egger intercept.

The MR Egger intercept showed no evidence for directional pleiotropy. Several phenotypes showed a significant MR-PRESSO global test. In this situation, outlier tests were run to correct for pleiotropic outliers. If distortion tests identified significantly different estimates following adjustment for outliers, then MR-PRESSO outlier corrected causal estimates are presented in Figure 3. Only the exposures BMI, waist circumference and HDL cholesterol had significant global tests and outlier tests.

Table S10. Linear regressions between BMI and subjective wellbeing in the UK Biobank sample

	Mean (SD)	Beta (95% CI)	N	p-value
Happiness	4.45 (0.70)	-0.001 (-0.002, -0.001)	110,347	0.002
Satisfaction with work	4.40 (0.87)	-0.001 (-0.002, 0.000)	75,519	0.097
Satisfaction with health	4.25 (0.87)	-0.048 (-0.047, -0.049)	110,388	<0.001
Satisfaction with finances	4.31 (0.94)	-0.021 (-0.020, -0.022)	110,247	<0.001
Satisfaction with friends	4.76 (0.74)	0.002 (0.001, 0.003)	109,550	0.001
Satisfaction with family	4.79 (0.90)	-0.000 (-0.001, 0.001)	109,712	0.938

Note. Means and standard deviations for the subjective wellbeing measures (scored from 1-6 with 6 being high wellbeing). Mean subjective wellbeing values show some negative skew but none have skew less than -1. Linear regressions were conducted to test the observational association between BMI and subjective wellbeing in our UK Biobank sample controlling for age, sex and SEP. BMI was negatively associated with all measures of subjective wellbeing apart from job satisfaction and satisfaction with family where there was no clear association and satisfaction with friends where the association was positive.

Table S11. Results of one-sample MR of BMI (exposure) on subjective wellbeing (outcome) in the independent UK Biobank sample controlling for age, sex and 10 principal components.

Outcome	Beta (95% CI)	P-value
Happiness	0.001 (-0.007, 0.009)	0.810
Satisfaction with work	0.005 (-0.007, 0.016)	0.417
Satisfaction with health	-0.037 (-0.046, -0.027)	<0.001
Satisfaction with finances	-0.003 (-0.014, 0.007)	0.516
Satisfaction with friends	0.003 (-0.005, 0.011)	0.515
Satisfaction with family	0.002 (-0.008, 0.012)	0.722

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