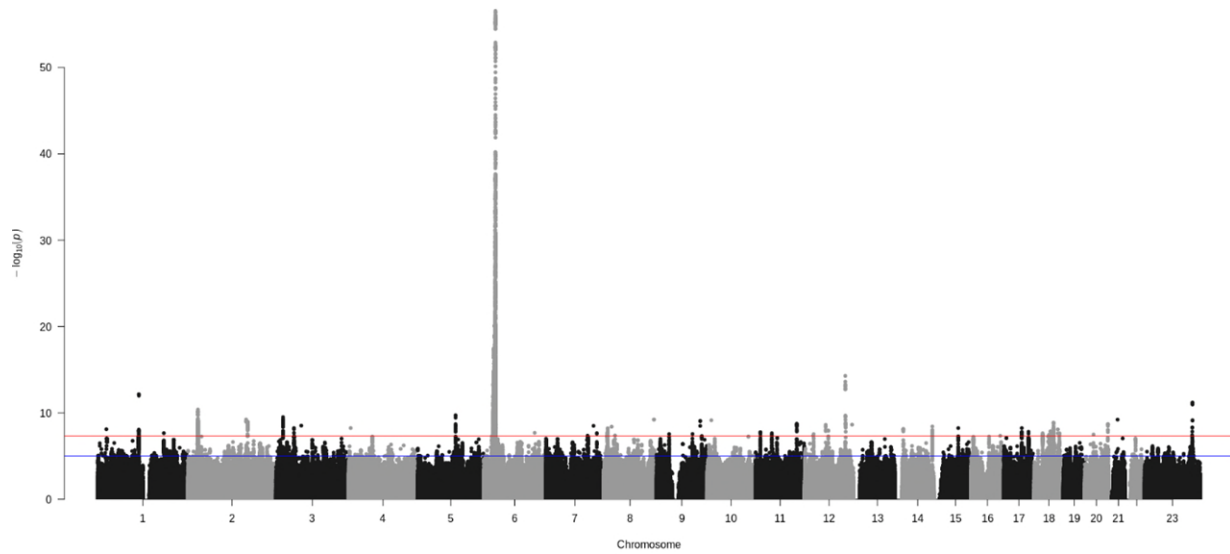


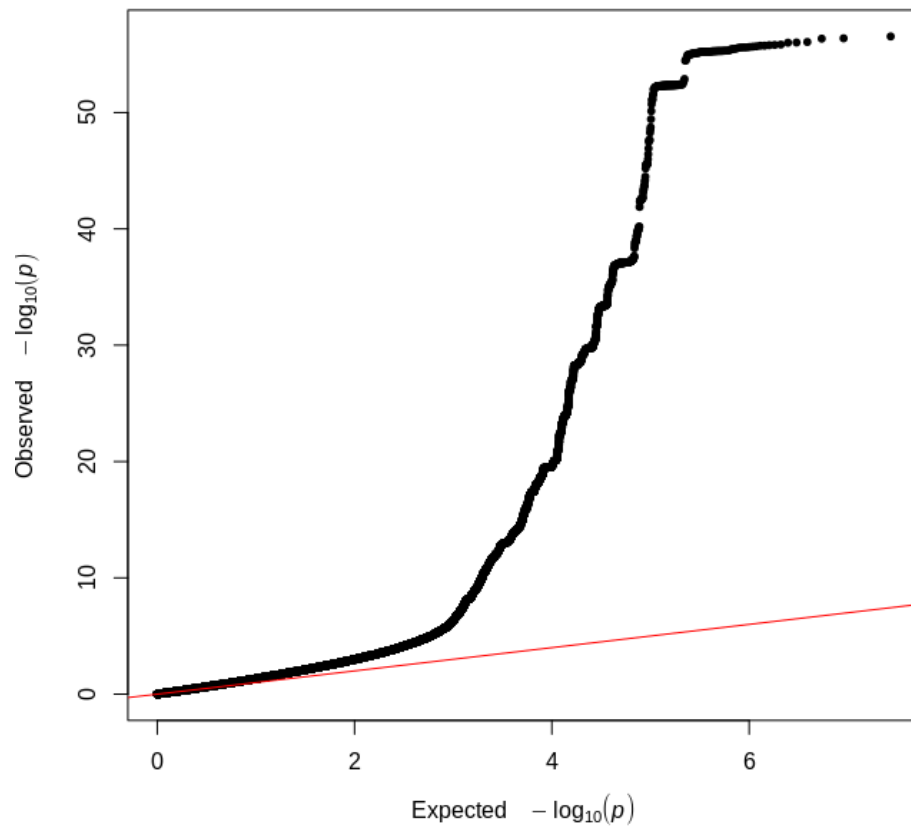
Supplementary Information

Supplementary Figures and Legends

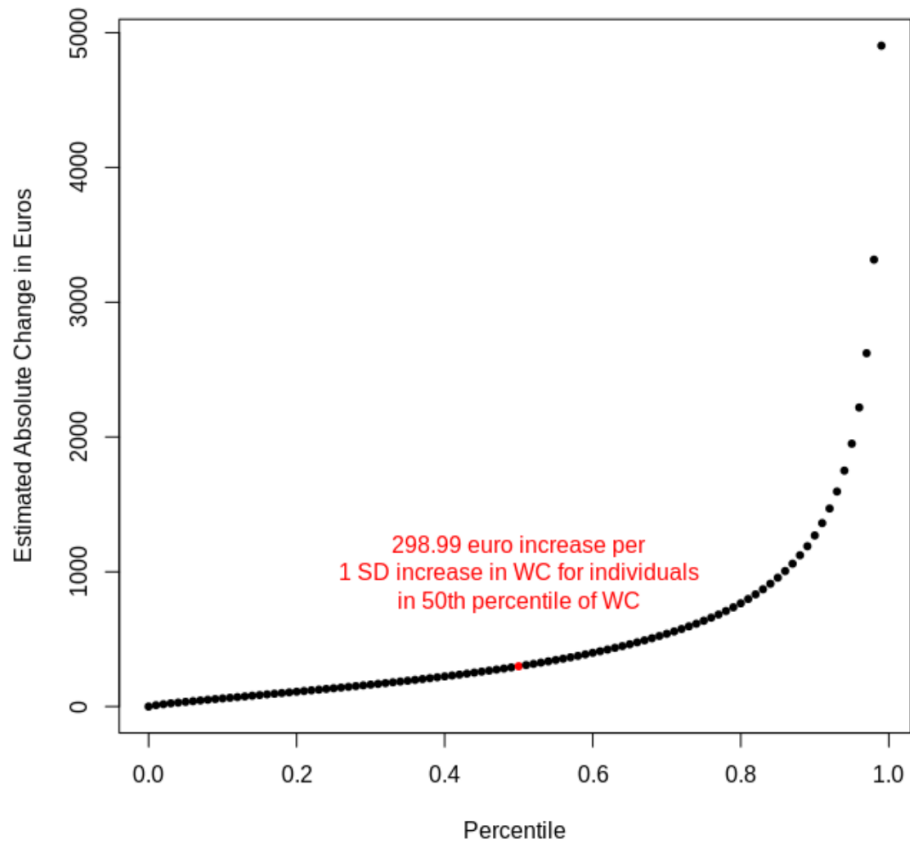
Supplementary Figure 1. Manhattan plot from GWAS of log-transformed annual total healthcare costs in FinnGen.



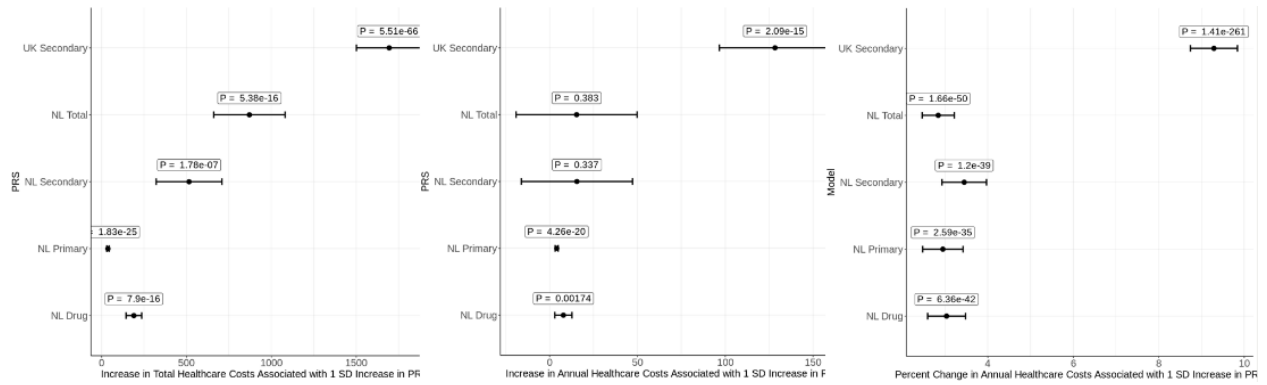
Supplementary Figure 2. Q-Q plot from GWAS of log-transformed annual total healthcare costs in FinnGen. Lambda 0.7 = 1.304, lambda 0.5 = 1.293, lambda 0.1 = 1.285, lambda 0.01 = 1.29, lambda 0.001 = 1.295.



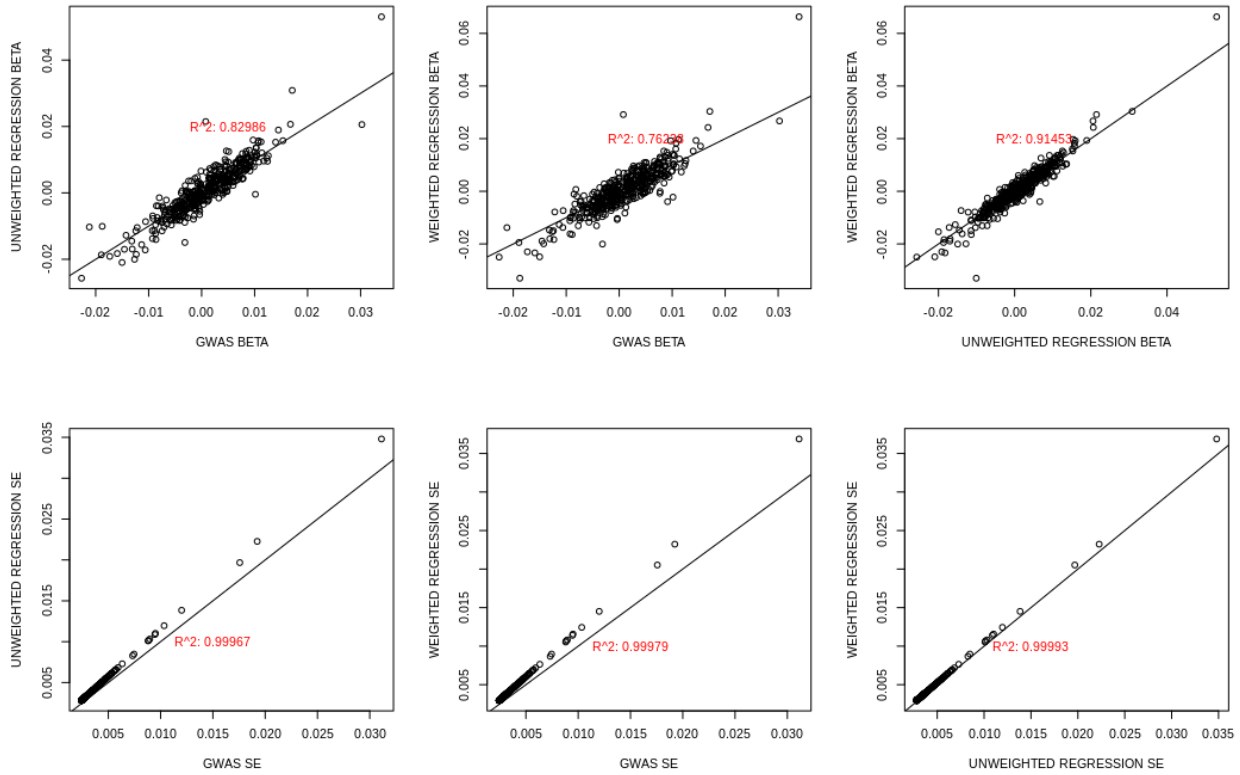
Supplementary Figure 3. Monetary impact of waist circumference for 343,160 FinnGen participants as estimated from Mendelian Randomization at varying baseline healthcare costs. SD is standard deviation. Red point indicates the healthcare costs calculated at the 50th percentile of waist circumference (WC).



Supplementary Figure 4. Polygenic score analysis between Finland, United Kingdom, and Netherlands for primary, secondary, medication, and total healthcare costs for total costs (A), total costs per year (B), and log total costs per year (C). Points indicate beta effect size estimates and bars indicate 95% confidence interval. Two-sided p-values were calculated from the effect estimates and standard errors of the Mendelian Randomization model and evaluated at alpha = 0.05 without adjustment for multiple testing hypothesis. UK = United Kingdom and NL = Netherlands.



Supplementary Figure 5. Correlation between GWAS- and weighted linear regression-based models in reweighted FinnGen cohort.



Supplementary Tables

Supplementary Table 1. Summary of summary statistics used as genetic instruments for exposures and mediators.

Phenotype	ID from MRC IEU OpenGWAS Database	Year	Sample size	Population	N SNPs available in sumstats	Unit	Transformation coefficient used to transform SD to raw units	Reference	N SNPs used in MR	R-square value	F-statistic
HDL cholesterol	ieu-a-299	2013	187167	Mixed	2447442	sd	1	http://lipidgenetics.org/	492	0.446178656	305.6735297
HDL cholesterol	ieu-a-299	2013	187167	Mixed	2447442	raw	15.51018433	http://lipidgenetics.org/	492	0.446178656	305.6735297
LDL cholesterol	ieu-a-300	2013	173082	Mixed	2437752	sd	1	http://lipidgenetics.org/	396	0.399169935	289.7114074
LDL cholesterol	ieu-a-300	2013	173082	Mixed	2437752	raw	38.6745912	http://lipidgenetics.org/	396	0.399169935	289.7114074
Triglycerides	ieu-a-302	2013	177861	Mixed	2439433	sd	1	http://lipidgenetics.org/	452	0.372324119	232.8201126
Triglycerides	ieu-a-302	2013	177861	Mixed	2439433	raw	90.72424257	http://lipidgenetics.org/	452	0.372324119	232.8201126
Waist circumference	ieu-a-61	2015	232101	European	2565408	sd	1	https://pubmed.ncbi.nlm.nih.gov/25673412/	42	0.01071664	59.85289658
Waist circumference	ieu-a-61	2015	232101	European	2565408	raw	12.52	https://pubmed.ncbi.nlm.nih.gov/25673412/	42	0.01071664	59.85289658
Body mass index	ieu-a-835	2015	322154	European	2554668	sd	1	https://www.nature.com/articles/nature14177	69	0.01429497	67.69495838
Body mass index	ieu-a-835	2015	322154	European	2554668	raw	4.77	https://www.nature.com/articles/nature14177	69	0.01429497	67.69495838
HDL cholesterol	ieu-b-109	2020	403943	European	12321875	sd	1	https://pubmed.ncbi.nlm.nih.gov/32203549/	362	0.135797258	175.1848019
HDL cholesterol	ieu-b-109	2020	403943	European	12321875	raw	0.323918	https://pubmed.ncbi.nlm.nih.gov/32203549/	362	0.135797258	175.1848019
Triglycerides	ieu-b-111	2020	441016	European	12321875	sd	1	https://pubmed.ncbi.nlm.nih.gov/32203549/	313	0.100635527	157.5492278
Triglycerides	ieu-b-111	2020	441016	European	12321875	raw	1.02441	https://pubmed.ncbi.nlm.nih.gov/32203549/	313	0.100635527	157.5492278
Systolic blood pressure	ieu-b-38	2018	757601	European	7088083	sd	1	https://pubmed.ncbi.nlm.nih.gov/30224653/	461	0.045387404	78.08774463
LDL cholesterol	ieu-b-110	2020	440546	European	12321875	sd	1	https://pubmed.ncbi.nlm.nih.gov/32203549/	177	0.069019757	184.4486365
LDL cholesterol	ieu-b-110	2020	440546	European	12321875	raw	0.434527	https://pubmed.ncbi.nlm.nih.gov/32203549/	177	0.069019757	184.4486365
Systolic blood pressure	ieu-b-38	2018	757601	European	7088083	raw	20.7	https://pubmed.ncbi.nlm.nih.gov/30224653/	461	0.045387404	78.08774463
Systolic blood pressure	ukb-a-360	2017	317754	European	10894596	sd	1	http://www.nealelab.is/uk-biobank	167	0.026764275	52.29766649
Systolic blood pressure	ukb-a-360	2017	317754	European	10894596	raw	19.3261	http://www.nealelab.is/uk-biobank	167	0.026764275	52.29766649
Waist circumference	ukb-a-382	2015	224459	European	2566630	sd	1	http://www.nealelab.is/uk-biobank	232	0.055958971	57.28973833
Waist circumference	ukb-a-382	2015	224459	European	2566630	raw	13.4212	http://www.nealelab.is/uk-biobank	232	0.055958971	57.28973833
Albumin	ukb-d-30600_irt	2018	385205	European	13585334	quantile	1	https://pan.ukbb.broadinstitute.org/	203	0.042273402	83.71272288
Albumin	ukb-d-30600_raw	2018	385205	European	13585334	raw	1	https://pan.ukbb.broadinstitute.org/	201	0.041610832	83.16346129
Alanine aminotransferase	ukb-d-30620_irt	2018	420449	European	13586000	quantile	1	https://pan.ukbb.broadinstitute.org/	207	0.040748095	86.23880263
Alanine aminotransferase	ukb-d-30620_raw	2018	420449	European	13586000	raw	1	https://pan.ukbb.broadinstitute.org/	125	0.025493342	87.96605344
Creatinine	ukb-d-30700_irt	2018	420401	European	13585973	quantile	1	https://pan.ukbb.broadinstitute.org/	337	0.067826081	90.69520111
Creatinine	ukb-d-30700_raw	2018	420401	European	13585973	raw	1	https://pan.ukbb.broadinstitute.org/	184	0.029946233	70.50195393
C-reactive protein	ukb-d-30710_irt	2018	419693	European	13586004	quantile	1	https://pan.ukbb.broadinstitute.org/	210	0.082240904	179.0000753
C-reactive protein	ukb-d-30710_raw	2018	419693	European	13586004	raw	1	https://pan.ukbb.broadinstitute.org/	53	0.017841629	143.831148
Cystatin C	ukb-d-30720_irt	2018	420588	European	13586047	quantile	1	https://pan.ukbb.broadinstitute.org/	312	0.109139841	165.0261413
Cystatin C	ukb-d-30720_raw	2018	420588	European	13586047	raw	1	https://pan.ukbb.broadinstitute.org/	196	0.062034264	141.8541338
Glucose	ukb-d-30740_irt	2018	384760	European	13585279	quantile	1	https://pan.ukbb.broadinstitute.org/	108	0.032547278	119.8196455
Glucose	ukb-d-30740_raw	2018	384760	European	13585279	raw	1	https://pan.ukbb.broadinstitute.org/	61	0.012404914	79.21454429
Glycated hemoglobin	ukb-d-30750_irt	2018	419434	European	13586180	quantile	1	https://pan.ukbb.broadinstitute.org/	320	0.106851885	156.6894856
Glycated hemoglobin	ukb-d-30750_raw	2018	419434	European	13586180	raw	1	https://pan.ukbb.broadinstitute.org/	190	0.046848766	108.4547446
Lipoprotein(a)	ukb-d-30790_irt	2018	335796	European	13583854	quantile	1	https://pan.ukbb.broadinstitute.org/	22	0.335032837	7689.715379
Lipoprotein(a)	ukb-d-30790_raw	2018	335796	European	13583854	raw	1	https://pan.ukbb.broadinstitute.org/	21	0.507893887	16502.20565
Vitamin D	ukb-d-30890_irt	2018	401516	European	13585763	quantile	1	https://pan.ukbb.broadinstitute.org/	59	0.036643376	258.8179126
Vitamin D	ukb-d-30890_raw	2018	401516	European	13585763	raw	1	https://pan.ukbb.broadinstitute.org/	65	0.039433759	253.5472881
Type 2 diabetes	ukb-a-306	2017	336473	European	10894596	sd	1	http://www.nealelab.is/uk-biobank	52	0.010261586	67.07682863
Back pain	ukb-a-473	2017	336650	European	10894596	sd	1	http://www.nealelab.is/uk-biobank	9	0.001084516	40.6097743
Chronic ischemic heart disease	ukb-a-534	2017	337199	European	10894596	sd	1	http://www.nealelab.is/uk-biobank	16	0.003125826	66.07982909
Chronic obstructive pulmonary disease	ukb-a-543	2017	337199	European	10894596	sd	1	http://www.nealelab.is/uk-biobank	2	0.000185913	31.35039071
Stroke	ukb-d-C_STROKE	2018	361194	European	12404026	binary	1	http://www.nealelab.is/uk-biobank	1	8.79E-05	31.76203333
Medication for cholesterol, blood pressure, diabetes, or take exogenous hormones: Blood pressure medication	ukb-b-18009	2018	294710	European	9851867	binary	1	http://www.nealelab.is/uk-biobank	96	0.02833243	56.81972

Supplementary Table 2. Top independent genome-wide significant hits from GWAS of healthcare costs in FinnGen performed using REGENIE. REGENIE fit a whole-genome regression model and performed single-variant association testing, which produces effect estimates, standard errors, and p-values of association between variants and outcomes. P-values were considered at genome-wide significant ($P < 5 \times 10^{-8}$) to adjust for multiple hypothesis testing.

chr	pos	rsid	ref	alt	pval	beta	se	eaf	info
1	24697088	rs144552623	A	G	7.77E-09	0.064115	0.011105	0.012629	0.962229
1	1.14E+08	rs6679677	C	A	6.92E-13	0.024785	0.003451	0.146586	0.999818
1	1.82E+08	rs11806150	A	G	2.19E-08	-0.02097	0.003747	0.121279	0.996973
2	27111756	rs2891550	C	T	4.14E-11	0.016507	0.002502	0.598099	0.990897
2	28211309	rs72818428	A	G	9.77E-10	0.02183	0.003571	0.135733	0.995658
2	1.59E+08	rs62173233	T	A	5.76E-10	-0.02558	0.004129	0.098028	0.98583
2	1.64E+08	rs1529997	C	T	1.06E-09	0.016677	0.002734	0.723271	0.995827
3	18741984	rs4532156	T	C	3.07E-10	0.016226	0.002577	0.657647	0.99458
3	48670914	rs73078367	C	T	5.64E-09	-0.01732	0.002973	0.214	0.998114
5	1.04E+08	rs2403304	T	C	1.90E-10	0.016368	0.00257	0.346732	0.996614
6	28708617	rs9366724	A	T	1.22E-13	0.032242	0.004348	0.086162	0.998889
6	31434633	rs6935045	T	A	4.52E-13	0.024974	0.00345	0.147252	0.997437
6	31521145	rs549105374	A	T	1.50E-17	-0.03054	0.003582	0.134512	0.996997
6	32624232	rs1281947	A	G	4.40E-57	0.054459	0.00342	0.150316	0.999619
6	32789325	rs9276710	T	C	1.38E-29	0.033907	0.003002	0.20858	0.998497
7	1.4E+08	rs4507685	T	A	2.22E-08	-0.01371	0.002451	0.455723	0.994841
8	10924932	rs4841459	A	C	5.93E-09	-0.01424	0.002446	0.45833	0.995976
8	30931118	rs2344118	C	A	4.11E-08	0.014402	0.002625	0.316921	0.995778
9	34424949	rs62559895	T	C	2.81E-08	0.017022	0.003066	0.199716	0.992107
9	98759624	rs192202574	C	T	2.76E-08	0.051645	0.009295	0.017675	0.994859
9	1.24E+08	rs944339	C	T	4.88E-08	0.013363	0.002449	0.482113	0.994298
11	13298291	rs6486116	A	C	1.75E-08	0.015295	0.002714	0.720071	0.999488
11	44706962	rs10838338	C	T	2.24E-08	-0.02581	0.004615	0.076855	0.986068
11	1.13E+08	rs1836798	A	G	1.91E-09	0.014821	0.002468	0.42046	0.997589
12	24275471	rs10842306	A	G	2.87E-08	-0.01362	0.002454	0.5458	0.998222
12	57584957	rs775251	C	T	2.38E-09	0.01531	0.002565	0.649326	0.994065
12	64702618	rs1690264	C	T	1.08E-08	0.014164	0.002477	0.474906	0.973555
12	1.11E+08	rs3184504	T	C	2.45E-14	-0.01893	0.002483	0.591367	0.999925
14	1.03E+08	rs8010932	A	G	3.77E-09	0.016796	0.00285	0.242823	0.997046
15	67165147	rs2289261	G	C	5.65E-09	0.014383	0.002468	0.57319	0.997683
16	80390010	rs12919036	A	G	4.44E-08	-0.01387	0.002534	0.378044	0.986577
17	49222427	rs55978930	A	G	5.61E-09	0.014792	0.002538	0.370926	0.990835
17	67896391	rs61676547	G	C	1.56E-08	0.016152	0.002856	0.24139	0.99716
18	23496800	rs303754	G	T	2.27E-08	0.013676	0.002447	0.502685	0.993587
18	41733420	rs67311948	T	C	3.51E-08	-0.02267	0.004111	0.097921	0.996927
18	53198529	rs62099231	G	A	1.34E-09	0.014859	0.002451	0.459507	0.998297
20	24379863	rs67976007	G	A	3.21E-08	-0.02409	0.004356	0.087054	0.988078
20	63951116	rs2320226	T	C	2.03E-09	-0.01514	0.002525	0.616045	0.989463

Supplementary Table 3. Full Mendelian Randomization results for all risk factors using all methods in Finland. Mendelian Randomization models produced effect estimates, standard errors, and p-values of causal effects of exposures and outcomes. P-values were adjusted for multiple hypothesis testing with the Bonferroni correction. Table was truncated at 100 rows. See Supplementary Tables for full table.

Exposure	Unit	Outcome	Method	N SNPs	Beta association	Standard error	P-value	Percent change	Confidence intervals for percentage change
Waist circumference	Raw unit	AvoHILMO	Inverse variance weighted	213	0.011647989	0.001533748	3.09E-14	1.17	[0.87, 1.48]
Waist circumference	1 SD	AvoHILMO	Inverse variance weighted	213	0.156329994	0.02058474	3.09E-14	16.92	[12.3, 21.73]
Waist circumference	1 SD	AvoHILMO	Inverse variance weighted	39	0.157797295	0.024504841	1.20E-10	17.09	[11.6, 22.85]
Waist circumference	Raw unit	AvoHILMO	Inverse variance weighted	39	0.012603618	0.001957256	1.20E-10	1.27	[0.88, 1.66]
Body mass index	Raw unit	AvoHILMO	Inverse variance weighted	66	0.024336386	0.004070851	2.26E-09	2.46	[1.65, 3.28]
Body mass index	1 SD	AvoHILMO	Inverse variance weighted	66	0.116084562	0.019417959	2.26E-09	12.31	[8.12, 16.67]
Waist circumference	1 SD	AvoHILMO	Weighted median	213	0.150655502	0.025483785	3.38E-09	16.26	[10.6, 22.21]
Waist circumference	Raw unit	AvoHILMO	Weighted median	213	0.011225189	0.001943269	7.63E-09	1.13	[0.74, 1.51]
Systolic blood pressure	Raw unit	AvoHILMO	Inverse variance weighted	426	0.000199395	3.55E-05	2.01E-08	0.02	[0.01, 0.03]
Systolic blood pressure	1 SD	AvoHILMO	Inverse variance weighted	426	0.004127469	0.000735555	2.01E-08	0.41	[0.27, 0.56]
Waist circumference	1 SD	AvoHILMO	Weighted median	39	0.161155417	0.031453443	3.00E-07	17.49	[10.46, 24.96]
Waist circumference	Raw unit	AvoHILMO	Weighted median	39	0.012871838	0.002556223	4.77E-07	1.3	[0.79, 1.8]
Systolic blood pressure	Raw unit	AvoHILMO	Weighted median	146	0.006214433	0.001294732	1.59E-06	0.62	[0.37, 0.88]
Systolic blood pressure	1 SD	AvoHILMO	Weighted median	146	0.120100759	0.025166939	1.82E-06	12.76	[7.33, 18.46]
Body mass index	Raw unit	AvoHILMO	Weighted median	66	0.025093864	0.005364229	2.90E-06	2.54	[1.47, 3.62]
Body mass index	1 SD	AvoHILMO	Weighted median	66	0.119697733	0.025846461	3.64E-06	12.72	[7.15, 18.57]
Systolic blood pressure	1 SD	AvoHILMO	Inverse variance weighted	146	0.097018559	0.020991154	3.80E-06	10.19	[5.75, 14.82]
Systolic blood pressure	Raw unit	AvoHILMO	Inverse variance weighted	146	0.00502008	0.001086156	3.80E-06	0.5	[0.29, 0.72]
Systolic blood pressure	Raw unit	AvoHILMO	Weighted median	426	0.000226627	4.95E-05	4.70E-06	0.02	[0.01, 0.03]
Systolic blood pressure	1 SD	AvoHILMO	Weighted median	426	0.004691178	0.001034961	5.82E-06	0.47	[0.27, 0.67]
Triglycerides	1 SD	AvoHILMO	Inverse variance weighted	420	0.048058292	0.011033777	1.33E-05	4.92	[2.68, 7.22]
Triglycerides	Raw unit	AvoHILMO	Inverse variance weighted	420	0.000529718	0.000121619	1.33E-05	0.05	[0.03, 0.08]
Alanine aminotransferase	1 SD	AvoHILMO	Inverse variance weighted	170	0.068380093	0.016138862	2.27E-05	7.08	[3.74, 10.52]
Alanine aminotransferase	Raw unit	AvoHILMO	Inverse variance weighted	102	0.005437255	0.001382758	8.42E-05	0.55	[0.27, 0.82]
C-reactive protein	Raw unit	AvoHILMO	Inverse variance weighted	39	0.017461588	0.004628387	0.000161481	1.76	[0.84, 2.69]
Glycated hemoglobin	Raw unit	AvoHILMO	Inverse variance weighted	145	0.008960515	0.002495543	0.000329908	0.9	[0.41, 1.39]
Systolic blood pressure	1 SD	AvoHILMO	MR Egger	426	0.006640303	0.001846283	0.000360413	0.67	[0.3, 1.03]
Systolic blood pressure	Raw unit	AvoHILMO	MR Egger	426	0.000320788	8.92E-05	0.000360413	0.03	[0.01, 0.05]
Waist circumference	Raw unit	AvoHILMO	Weighted mode	213	0.012438049	0.003439055	0.000372937	1.25	[0.57, 1.94]
HDL cholesterol	1 SD	AvoHILMO	Inverse variance weighted	445	-0.035585528	0.010071605	0.00041048	-3.5	[-5.38, -1.57]
HDL cholesterol	Raw unit	AvoHILMO	Inverse variance weighted	445	-0.002294333	0.000649354	0.00041048	-0.23	[-0.36, -0.1]
Waist circumference	1 SD	AvoHILMO	Weighted mode	213	0.166933546	0.047948933	0.000605406	18.17	[7.57, 29.81]
Waist circumference	1 SD	AvoHILMO	MR Egger	213	0.22081111	0.063593569	0.000626058	24.71	[10.09, 41.26]
Waist circumference	Raw unit	AvoHILMO	MR Egger	213	0.016452412	0.004738292	0.000626058	1.66	[0.72, 2.61]
Cystatin C	1 SD	AvoHILMO	Inverse variance weighted	269	0.03052467	0.009180438	0.000884285	3.1	[1.26, 4.97]
Waist circumference	Raw unit	AvoHILMO	Weighted mode	39	0.021059733	0.00588448	0.0009631	2.13	[0.96, 3.31]
C-reactive protein	1 SD	AvoHILMO	Inverse variance weighted	179	0.034401483	0.010538926	0.001097619	3.5	[1.38, 5.66]
Waist circumference	Raw unit	AvoHILMO	Simple mode	39	0.021059733	0.00605371	0.001279398	2.13	[0.92, 3.35]
Cystatin C	Raw unit	AvoHILMO	Inverse variance weighted	166	0.21675076	0.068627916	0.001586667	24.2	[8.57, 42.09]
Waist circumference	1 SD	AvoHILMO	Weighted mode	39	0.263667854	0.077663751	0.001619041	30.17	[11.79, 51.57]
Systolic blood pressure	1 SD	AvoHILMO	Weighted mode	146	0.163766191	0.051578686	0.001829953	17.79	[6.47, 30.32]
Body mass index	1 SD	AvoHILMO	MR Egger	66	0.187071412	0.057559055	0.001841054	20.57	[7.71, 34.97]
Body mass index	Raw unit	AvoHILMO	MR Egger	66	0.039218325	0.012066888	0.001841054	4	[1.57, 6.49]
Waist circumference	1 SD	AvoHILMO	Simple mode	39	0.263667854	0.079831788	0.002091859	30.17	[11.32, 52.22]
Alanine aminotransferase	1 SD	AvoHILMO	Weighted median	170	0.060633163	0.019981172	0.002409229	6.25	[2.17, 10.49]
HDL cholesterol	Raw unit	AvoHILMO	Inverse variance weighted	308	-0.093564365	0.030922704	0.002480174	-8.93	[-14.29, -3.24]
HDL cholesterol	1 SD	AvoHILMO	Inverse variance weighted	308	-0.030307182	0.01001642	0.002480174	-2.99	[-4.87, -1.06]

Glycated hemoglobin	1 SD	AvoHILMO	Inverse variance weighted	256	0.030018343	0.010001361	0.002687186	3.05	[1.05, 5.09]
Body mass index	1 SD	AvoHILMO	Weighted mode	66	0.164177212	0.052978758	0.002868895	17.84	[6.22, 30.74]
Systolic blood pressure	Raw unit	AvoHILMO	Weighted mode	146	0.008473835	0.002843404	0.003379167	0.85	[0.29, 1.41]
Body mass index	Raw unit	AvoHILMO	Weighted mode	66	0.034418703	0.011901304	0.005201318	3.5	[1.12, 5.94]
Systolic blood pressure	Raw unit	AvoHILMO	Weighted mode	426	0.000280712	0.000100328	0.00537648	0.03	[0.01, 0.05]
C-reactive protein	Raw unit	AvoHILMO	MR Egger	39	0.020908101	0.007267671	0.006630153	2.11	[0.67, 3.58]
C-reactive protein	1 SD	AvoHILMO	Weighted mode	179	0.026700055	0.009748048	0.006789337	2.71	[0.76, 4.69]
Systolic blood pressure	1 SD	AvoHILMO	Weighted mode	426	0.005810747	0.002143533	0.006983442	0.58	[0.16, 1.01]
Systolic blood pressure	Raw unit	AvoHILMO	Simple mode	146	0.008473835	0.003225941	0.009545988	0.85	[0.22, 1.49]
Triglycerides	Raw unit	AvoHILMO	Inverse variance weighted	274	0.02603929	0.010680411	0.014767064	2.64	[0.51, 4.81]
Triglycerides	1 SD	AvoHILMO	Inverse variance weighted	274	0.026674909	0.01094112	0.014767064	2.7	[0.52, 4.93]
Waist circumference	1 SD	AvoHILMO	MR Egger	39	0.211799582	0.086399014	0.019073604	23.59	[4.34, 46.4]
Waist circumference	Raw unit	AvoHILMO	MR Egger	39	0.0169169	0.00690088	0.019073604	1.71	[0.34, 3.09]
Systolic blood pressure	1 SD	AvoHILMO	Simple mode	146	0.163766191	0.069151801	0.019193436	17.79	[2.86, 34.89]
Triglycerides	Raw unit	AvoHILMO	Simple mode	420	0.00090712	0.000407746	0.026631999	0.09	[0.01, 0.17]
HDL cholesterol	Raw unit	AvoHILMO	Simple mode	445	-0.004500776	0.002041394	0.027983305	-0.45	[-0.85, -0.05]
HDL cholesterol	1 SD	AvoHILMO	Simple mode	445	-0.069807863	0.032886841	0.03433444	-6.74	[-12.56, -0.53]
Cystatin C	Raw unit	AvoHILMO	Weighted mode	166	0.154710816	0.073771966	0.03750487	16.73	[1.02, 34.89]
Triglycerides	1 SD	AvoHILMO	Simple mode	420	0.082297792	0.040471129	0.042632313	8.58	[0.3, 17.54]
Body mass index	Raw unit	AvoHILMO	Simple mode	66	0.025985283	0.012660946	0.044162024	2.63	[0.12, 5.21]
Body mass index	1 SD	AvoHILMO	Simple mode	66	0.1239498	0.060796689	0.045545247	13.2	[0.48, 27.52]
Systolic blood pressure	1 SD	AvoHILMO	Simple mode	426	0.006138355	0.003094908	0.047968989	0.62	[0.01, 1.23]
Triglycerides	1 SD	AvoHILMO	Weighted mode	420	0.027519008	0.014241992	0.054003135	2.79	[-0.04, 5.7]
Glucose	1 SD	AvoHILMO	Weighted median	88	-0.039584478	0.020723638	0.056118744	-3.88	[-7.71, 0.1]
Systolic blood pressure	1 SD	AvoHILMO	MR Egger	146	0.134657275	0.070006482	0.05639087	14.41	[-0.26, 31.24]
Systolic blood pressure	Raw unit	AvoHILMO	MR Egger	146	0.006967638	0.00362238	0.05639087	0.7	[-0.01, 1.42]
Cystatin C	Raw unit	AvoHILMO	MR Egger	166	0.186798752	0.097377382	0.056810655	20.54	[-0.41, 45.89]
Cystatin C	1 SD	AvoHILMO	Weighted mode	269	0.018803357	0.010083979	0.063319807	1.9	[-0.1, 3.93]
Triglycerides	Raw unit	AvoHILMO	Weighted mode	420	0.000303326	0.000164404	0.065742327	0.03	[0, 0.06]
C-reactive protein	Raw unit	AvoHILMO	Weighted median	39	0.012220736	0.006664778	0.066708931	1.23	[-0.08, 2.56]
Systolic blood pressure	Raw unit	AvoHILMO	Simple mode	426	0.000296539	0.000162894	0.069395211	0.03	[0, 0.06]
Alanine aminotransferase	1 SD	AvoHILMO	Weighted mode	170	0.050719316	0.028048354	0.072340531	5.2	[-0.42, 11.15]
Glucose	Raw unit	AvoHILMO	Inverse variance weighted	52	0.046461514	0.026508185	0.079649511	4.76	[-0.55, 10.34]
C-reactive protein	1 SD	AvoHILMO	Weighted median	179	0.026135799	0.015474028	0.091217377	2.65	[-0.42, 5.81]
Cystatin C	Raw unit	AvoHILMO	Weighted median	166	0.125643426	0.074530989	0.091836694	13.39	[-2.02, 31.22]
LDL cholesterol	Raw unit	AvoHILMO	Weighted mode	151	-0.048593807	0.029189058	0.098041022	-4.74	[-10.04, 0.87]
Waist circumference	Raw unit	AvoHILMO	Simple mode	213	0.009188448	0.005572568	0.100655004	0.92	[-0.17, 2.03]
Alanine aminotransferase	1 SD	AvoHILMO	MR Egger	170	0.049404603	0.029931856	0.100694782	5.06	[-0.92, 11.41]
Cystatin C	1 SD	AvoHILMO	Weighted median	269	0.017123649	0.010447336	0.101204	1.73	[-0.33, 3.83]
C-reactive protein	1 SD	AvoHILMO	MR Egger	179	0.024003723	0.014585055	0.101584604	2.43	[-0.46, 5.4]
LDL cholesterol	1 SD	AvoHILMO	Weighted mode	151	-0.021115321	0.013012947	0.106766383	-2.09	[-4.56, 0.44]
Triglycerides	Raw unit	AvoHILMO	Weighted mode	274	0.019876159	0.012436571	0.111154657	2.01	[-0.45, 4.52]
Cystatin C	1 SD	AvoHILMO	MR Egger	269	0.0203131	0.012711973	0.111236788	2.05	[-0.46, 4.63]
Triglycerides	1 SD	AvoHILMO	Weighted mode	274	0.020361336	0.01274873	0.11139432	2.06	[-0.46, 4.64]
Waist circumference	1 SD	AvoHILMO	Simple mode	213	0.123320002	0.077599028	0.11350652	13.12	[-2.84, 31.71]
LDL cholesterol	Raw unit	AvoHILMO	Weighted median	359	-0.000591731	0.00038365	0.122982963	-0.06	[-0.13, 0.02]
LDL cholesterol	1 SD	AvoHILMO	MR Egger	359	-0.025231894	0.016400426	0.124814649	-2.49	[-5.58, 0.69]
LDL cholesterol	Raw unit	AvoHILMO	MR Egger	359	-0.000652415	0.000424062	0.124814649	-0.07	[-0.15, 0.02]
HDL cholesterol	1 SD	AvoHILMO	Weighted mode	308	-0.01997558	0.01312873	0.129159539	-1.98	[-4.47, 0.58]
Alanine aminotransferase	1 SD	AvoHILMO	Simple mode	170	0.071356397	0.046872315	0.129788585	7.4	[-2.03, 17.73]
HDL cholesterol	Raw unit	AvoHILMO	Weighted mode	308	-0.061686834	0.041015775	0.13372925	-5.98	[-13.24, 1.89]
LDL cholesterol	1 SD	AvoHILMO	Weighted median	359	-0.022884947	0.015567028	0.141537119	-2.26	[-5.2, 0.77]

Supplementary Table 4. Mendelian Randomization replication results in the United Kingdom and Netherlands. Mendelian Randomization models produced effect estimates, standard errors, and p-values of causal effects of exposures and outcomes. P-values were adjusted for multiple hypothesis testing with the Bonferroni correction.

Phenotype	Country	Effect size	Unit for effect size	Confidence interval for effect size	P-value	Monetary effect	Unit for monetary effect
WC	UK	13.62	cm	[11.66, 15.58]	3.13E-42	162.0849697	per 10 cm
WC	UK	182.82	SD	[156.51, 209.13]	3.13E-42	217.5651553	per SD
WC	UK	7.94	cm	[4.99, 10.89]	1.33E-07	94.49006307	per 10 cm
WC	UK	99.37	SD	[62.44, 136.30]	1.33E-07	118.255385	per SD
BMI	UK	18.66	kg/m ²	[11.54, 25.79]	2.87E-07	111.0317744	per 5 kg/m ²
BMI	UK	89.03	SD	[55.03, 123.03]	2.87E-07	105.9502559	per SD
SBP	UK	0.06	mmHg	[0.009, 0.12]	2.27E-02	0.714030703	per 10 mmHg
SBP	UK	1.30	SD	[0.18, 2.42]	2.27E-02	1.547066524	per SD
SBP	UK	0.74	mmHg	[-0.75, 2.24]	3.31E-01	8.806378674	per 10 mmHg
SBP	UK	14.33	SD	[-14.57, 43.22]	3.31E-01	17.0534333	per SD
WC	NL	0.80	cm	[0.03, 1.57]	4.11E-02	129.907936	per 10 cm
WC	NL	11.24	SD	[0.43, 23.21]	4.11E-02	182.5206501	per SD
WC	NL	0.81	cm	[-0.39, 2.02]	1.85E-01	131.5317852	per 10 cm
WC	NL	10.63	SD	[-4.72, 28.45]	1.85E-01	172.61517	per SD
BMI	NL	3.22	kg/m ²	[0.59, 5.91]	1.60E-02	261.4397212	per 5 kg/m ²
BMI	NL	16.31	SD	[2.86, 31.52]	1.60E-02	264.8498045	per SD
SBP	NL	0.03	mmHg	[0.01, 0.05]	7.69E-03	4.8715476	per 10 mmHg
SBP	NL	0.62	SD	[0.16, 1.08]	7.69E-03	10.06786504	per SD
SBP	NL	0.54	mmHg	[-0.10, 1.190]	9.75E-02	87.6878568	per 10 mmHg
SBP	NL	11.00	SD	[-1.89, 25.59]	9.75E-02	178.623412	per SD

Supplementary Table 5. Genetic correlation between Finland, United Kingdom, and Netherlands calculated using LDSC. LDSC calculated genetic correlation based on the deviation between chi-square statistics compared to the expected deviation assuming the null hypothesis.

Country	Cost	Total observed scale h2 (standard error)	Lambda GC	Mean chi ²	Intercept (standard error)	Ratio
FI	Total	0.0649 (0.0034)	1.6831	1.7576	1.2246 (0.0182)	0.2965 (0.024)
FI	Primary care	0.0298 (0.0027)	1.3824	1.4025	1.1589 (0.013)	0.3971 (0.0323)
FI	Secondary care	0.0511 (0.0018)	1.4998	1.5337	1.1604 (0.0099)	0.3006 (0.0185)
FI	Medication	0.0706 (0.0036)	1.7491	1.8654	1.2828 (0.0189)	0.3268 (0.0219)
UK	Secondary care	0.0168 (0.0018)	1.0957	1.118	1.0177 (0.007)	0.1499 (0.0592)
NL	Total	-0.004 (0.0346)	1.0195	1.0231	1.0244 (0.0083)	1.0563 (0.3572)
NL	Primary care	0.0451 (0.0368)	0.9668	0.9941	0.9794 (0.0087)	NA (mean chi ² < 1)
NL	Secondary care	-0.0015 (0.0362)	1.0046	1.0046	1.0051 (0.0083)	1.1073 (1.7785)
NL	Medication	-0.0059 (0.0354)	1.0315	1.0275	1.0294 (0.0088)	1.0686 (0.3192)

Comparison	Genetic correlation	Stanford error	Z-score	P-value
FI-UK secondary care cost	0.804	0.05492	14.64	1.61E-48
FI-NL total cost	NA	NA	NA	NA
FI-NL primary care cost	0.7694	0.3387	2.2717	0.0231
FI-NL secondary care cost	NA	NA	NA	NA
FI-NL medication cost	NA	NA	NA	NA

Supplementary Table 6. Mendelian Randomization results for reweighted FinnGen cohort. Mendelian Randomization models produced effect estimates, standard errors, and p-values of causal effects of exposures and outcomes. P-values were adjusted for multiple hypothesis testing with the Bonferroni correction.

Exposure	Method	N SNPs	Beta association	Standard error	P-value	Percent change	Confidence interval for percent change
Waist circumference	Inverse variance weighted	192	0.204104803	0.024728054	1.53E-16	22.64	[16.84, 28.73]
Waist circumference	Inverse variance weighted	192	0.015207642	0.001842462	1.53E-16	1.53	[1.17, 1.9]
Body mass index	Inverse variance weighted	63	0.14635652	0.02178195	1.83E-11	15.76	[10.92, 20.81]
Body mass index	Inverse variance weighted	63	0.030682709	0.004566447	1.83E-11	3.12	[2.2, 4.04]
Waist circumference	Weighted median	192	0.184488193	0.028344169	7.57E-11	20.26	[13.76, 27.13]
Waist circumference	Weighted median	192	0.013746028	0.002138211	1.29E-10	1.38	[0.96, 1.81]
Waist circumference	Weighted mode	192	0.206982907	0.041381119	1.28E-06	23	[13.41, 33.39]
Body mass index	Weighted median	63	0.117052329	0.025401271	4.06E-06	12.42	[6.96, 18.16]
Waist circumference	Weighted mode	192	0.015422086	0.003272279	4.69E-06	1.55	[0.9, 2.21]
Body mass index	Weighted median	63	0.024539272	0.005363483	4.76E-06	2.48	[1.41, 3.57]
Systolic blood pressure	Weighted median	130	0.006124076	0.001363666	7.09E-06	0.61	[0.35, 0.88]
Systolic blood pressure	Inverse variance weighted	130	0.120259456	0.027410286	1.15E-05	12.78	[6.88, 19]
Systolic blood pressure	Inverse variance weighted	130	0.006222645	0.001418304	1.15E-05	0.62	[0.34, 0.9]
Systolic blood pressure	Weighted median	130	0.118354501	0.027492358	1.67E-05	12.56	[6.66, 18.8]
Waist circumference	Simple mode	192	0.268090753	0.073968057	0.000371312	30.75	[13.1, 51.14]
Waist circumference	Simple mode	192	0.01997517	0.00572225	0.000598077	2.02	[0.88, 3.17]
Body mass index	Weighted mode	63	0.023356732	0.007814773	0.004010823	2.36	[0.81, 3.94]
Body mass index	Weighted mode	63	0.111411612	0.037986043	0.00469967	11.79	[3.77, 20.43]
Systolic blood pressure	MR Egger	130	0.013284226	0.004759922	0.006062174	1.34	[0.4, 2.29]
Systolic blood pressure	MR Egger	130	0.256732277	0.091990722	0.006062174	29.27	[7.94, 54.81]
Body mass index	MR Egger	63	0.031606496	0.013524084	0.022735747	3.21	[0.51, 5.98]
Body mass index	MR Egger	63	0.150762988	0.06450988	0.022735747	16.27	[2.46, 31.94]
Waist circumference	MR Egger	192	0.146678628	0.074351379	0.049971493	15.8	[0.1, 33.96]
Waist circumference	MR Egger	192	0.010928876	0.005539846	0.049971493	1.1	[0.01, 2.2]
Systolic blood pressure	Weighted mode	130	0.109025055	0.055728594	0.052583655	11.52	[-0.02, 24.39]
Systolic blood pressure	Weighted mode	130	0.005641338	0.002964857	0.05930383	0.57	[-0.02, 1.15]
Body mass index	Simple mode	63	0.088251411	0.054838629	0.112632844	9.23	[-1.9, 21.62]
Body mass index	Simple mode	63	0.018501344	0.012057474	0.130011593	1.87	[-0.51, 4.3]
Systolic blood pressure	Simple mode	130	0.022490297	0.076250349	0.768503662	2.27	[-11.92, 18.76]
Systolic blood pressure	Simple mode	130	0.001163727	0.004103274	0.777164468	0.12	[-0.69, 0.92]

Supplementary Table 7. Multivariable Mendelian Randomization results. Mendelian Randomization models produced effect estimates, standard errors, and p-values of causal effects of exposures and outcomes. P-values were adjusted for multiple hypothesis testing with the Bonferroni correction.

Exposure (adjustment)	N SNPs	Beta association	Standard error	P-value	Percent change	Confidence interval for percent change
Systolic blood pressure	146	0.122910265	0.019480779	2.80E-10	13.08	[8.84, 17.48]
Systolic blood pressure (Back pain)	141	0.137259865	0.019481943	1.85E-12	14.71	[10.41, 19.18]
Systolic blood pressure (Back pain)	6	0.402395219	0.165252438	0.014890412	49.54	[8.17, 106.74]
Systolic blood pressure (Chronic ischemic heart disease)	140	0.117040775	0.020656652	1.46E-08	12.42	[7.96, 17.06]
Systolic blood pressure (Chronic ischemic heart disease)	9	0.490443393	0.325946778	0.132408108	63.3	[-13.79, 209.35]
Systolic blood pressure (Type 2 diabetes)	31	0.562597966	0.179663404	0.001739751	75.52	[23.42, 149.61]
Systolic blood pressure (Type 2 diabetes)	134	0.117334121	0.023976784	9.90E-07	12.45	[7.29, 17.86]
Systolic blood pressure (Chronic obstructive pulmonary disease)	142	0.123009287	0.020044428	8.42E-10	13.09	[8.73, 17.62]
Systolic blood pressure (Chronic obstructive pulmonary disease)	0	1.530639761	2.501787549	0.540657887	362.11	[-96.57, 62174.89]
Systolic blood pressure (Stroke)	142	0.090795774	0.020723857	1.18E-05	9.5	[5.15, 14.04]
Systolic blood pressure (Stroke)	1	3.655106515	0.911265608	6.05E-05	3767.16	[548.2, 22971.59]
Systolic blood pressure (Blood pressure medication)	127	0.037374119	0.031720892	0.238709803	3.81	[-2.45, 10.47]
Systolic blood pressure (Blood pressure medication)	68	0.23510217	0.086576174	0.006616523	26.5	[6.76, 49.9]
Systolic blood pressure (All)	27	0.459606406	0.158018571	0.003630981	58.35	[16.17, 115.83]
Systolic blood pressure (All)	120	0.055467051	0.036945512	0.133272706	5.7	[-1.68, 13.64]
Systolic blood pressure (All)	4	0.532909462	0.17123401	0.001857171	70.39	[21.81, 138.34]
Systolic blood pressure (All)	9	-0.033505085	0.355652629	0.924944462	-3.3	[-51.84, 94.17]
Systolic blood pressure (All)	0	2.76283842	2.189933536	0.207089753	1484.48	[-78.33, 115776.28]
Systolic blood pressure (All)	66	0.084097545	0.109622199	0.442987594	8.77	[-12.26, 34.85]
Systolic blood pressure (All)	0	3.087092868	0.986816671	0.001757998	2091.33	[216.75, 15060.12]
Body mass index	66	0.127848707	0.015407011	1.06E-16	13.64	[10.26, 17.12]
Body mass index (Back pain)	65	0.116856782	0.015456526	4.02E-14	12.4	[9.04, 15.85]
Body mass index (Back pain)	6	0.365900745	0.147175881	0.012913493	44.18	[8.05, 92.39]
Body mass index (Chronic ischemic heart disease)	62	0.12234999	0.018034934	1.17E-11	13.01	[9.09, 17.98]
Body mass index (Chronic ischemic heart disease)	10	0.244999483	0.316010902	0.438169457	27.76	[-31.23, 137.35]
Body mass index (Type 2 diabetes)	62	0.096968449	0.025180776	0.000117688	10.18	[4.88, 15.76]
Body mass index (Type 2 diabetes)	30	0.745895457	0.177961409	2.77E-05	110.83	[48.75, 198.83]
Body mass index (Chronic obstructive pulmonary disease)	65	0.126470693	0.015609499	5.40E-16	13.48	[10.06, 17.01]
Body mass index (Chronic obstructive pulmonary disease)	0	0.497060147	2.969990629	0.86708613	64.39	[-99.51, 55359.7]
Body mass index (Stroke)	65	0.128663231	0.015907781	6.06E-16	13.73	[10.24, 17.33]
Body mass index (Stroke)	0	-0.753460968	1.153163733	0.513507502	-52.93	[-95.09, 351.2]
Body mass index (Blood pressure medication)	54	0.096598673	0.020035366	1.43E-06	10.14	[5.9, 14.55]
Body mass index (Blood pressure medication)	60	0.389751186	0.055064039	1.46E-12	47.66	[32.55, 64.49]
Body mass index (All)	51	0.054651821	0.023755587	0.021414921	5.62	[0.81, 10.65]
Body mass index (All)	21	0.721296717	0.17124299	2.53E-05	105.71	[47.06, 187.75]
Body mass index (All)	4	0.703705715	0.201349662	0.000474162	102.12	[36.21, 199.92]
Body mass index (All)	6	-0.518399586	0.419436346	0.216479601	-40.45	[-73.83, 35.49]
Body mass index (All)	0	8.132679532	2.652704695	0.002170837	340290.82	[1779.1, 61660204.62]
Body mass index (All)	55	0.265555042	0.080976154	0.001040197	30.42	[11.28, 52.85]
Body mass index (All)	0	3.089070444	1.188020459	0.009317409	2095.67	[113.95, 22433.55]
Waist circumference	213	0.205264091	0.01703222	1.90E-33	22.78	[18.75, 26.95]
Waist circumference (Back pain)	206	0.169971559	0.019454333	2.39E-18	18.53	[14.09, 23.13]
Waist circumference (Back pain)	4	0.501044255	0.146122812	0.000605976	65.04	[23.94, 119.78]
Waist circumference (Chronic ischemic heart disease)	203	0.197124449	0.0178098	1.79E-28	21.79	[17.61, 26.12]
Waist circumference (Chronic ischemic heart disease)	10	0.505251208	0.330006304	0.125760738	65.74	[-13.2, 216.47]
Waist circumference (Type 2 diabetes)	32	0.691777821	0.155635892	8.80E-06	99.73	[47.22, 170.97]
Waist circumference (Type 2 diabetes)	191	0.164263405	0.02199847	8.20E-14	17.85	[12.88, 23.05]
Waist circumference (Chronic obstructive pulmonary disease)	207	0.20605183	0.018255047	1.51E-29	22.88	[18.56, 27.36]
Waist circumference (Chronic obstructive pulmonary disease)	1	-0.850323672	1.873014039	0.649838319	-57.27	[-98.91, 157.9]
Waist circumference (Stroke)	207	0.195786294	0.018089207	2.67E-27	21.63	[17.39, 26.02]
Waist circumference (Stroke)	1	1.208105223	0.806721981	0.134250618	234.71	[-31.14, 1526.93]
Waist circumference (Blood pressure medication)	170	0.163119674	0.018305122	5.05E-19	17.72	[13.57, 22.02]
Waist circumference (Blood pressure medication)	62	0.404518534	0.054841948	1.63E-13	49.86	[34.59, 66.86]
Waist circumference (All)	26	0.555951057	0.157005888	0.000398679	74.36	[28.17, 137.19]
Waist circumference (All)	156	0.082306721	0.025058516	0.001021342	8.58	[3.37, 14.04]
Waist circumference (All)	3	0.605319527	0.162586242	0.00196817	83.18	[33.2, 151.93]
Waist circumference (All)	10	0.102440911	0.344415221	0.766134936	10.79	[-43.6, 117.6]
Waist circumference (All)	0	0.90511267	2.041623798	0.657527204	147.22	[-95.48, 13419.19]
Waist circumference (All)	59	0.304253238	0.069347137	1.15E-05	35.56	[-18.33, 55.3]
Waist circumference (All)	0	2.029282307	0.840352109	0.01574385	660.86	[46.55, 3850.28]

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