

## Supplementary Figures and Tables

**Supplementary Table 1.** Results from the fixed-effects and random effects meta-analysis of the instruments. Sun et al. used simple linear regression using an additive genetic model for the test statistic. Ferkingstad et al. used linear mixed model implemented in BOLT-LMM for the test statistic. Pietzner et al. used BGENIE to perform a linear association test. Note: EA = Effect allele, OA = Other allele, SE = Standard error.

SNP	EA	OA	Beta			SE			Effect		SE		P-Value	Random	Heterogeneity			Sample size
			Sun et al. 2018	Ferkingstad et al., 2021	Pietzner et al., 2021	Sun et al. 2018	Ferkingstad et al., 2021	Pietzner et al., 2021	Fixed	Random	Fixed	Random			I <sup>2</sup>	Q statistic	Q P-Value	
rs7220711	A	G	0.0225	0.0323	0.0661	0.0255	0.00863	0.0125	0.042	0.04303	0.006842	0.013383	1.11E-09	0.00131	0.640486	5.563072	0.061943	49,372
rs66838809	A	G	-0.0833	-0.0462	-0.12	0.0485	0.0137	0.0232	-0.07	-0.08054	0.011478	0.028263	7.76E-09	0.00439	0.737024	7.605257	0.022312	49,372

**Supplementary Table 2.** Linkage disequilibrium correlation matrix of the instruments. The matrix was calculated using 1000 genomes LD European reference panel. Notice that the values correspond to r, not r<sup>2</sup>.

SNP	rs7220711 (G-A)	rs66838809 (A-G)
rs7220711 (G-A)	1	0.376
rs66838809 (A-G)	0.376	1

**Supplementary Table 3.** Results of the Mendelian randomisation of the positive control outcomes. MR estimates have been calculated using generalised inverse variance weighted method.

Outcome	N instruments	Type of estimate	MR estimate	Standard error	P value	GWAS ID
Heel bone mineral density	2	Beta [SD change/SD decrease in sclerostin levels]	1.00187062	0.04024844	9.05E-137	<a href="https://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST006001-GCST007000/GCST006979/">https://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST006001-GCST007000/GCST006979/</a>
Hip fracture	2	OR / SD decrease in sclerostin levels	0.15877783	0.33005603	2.46725E-08	<a href="http://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST90161001-GCST90162000/GCST90161240/">http://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST90161001-GCST90162000/GCST90161240/</a>

**Supplementary Table 4.** Results of the Mendelian randomisation of the GWAS outcomes. MR estimates have been calculated using generalised inverse variance weighted method.

Outcome	N instrument s	Type of estimate	MR estimate	Standard error	P value	GWAS ID
LDL cholesterol	2	Beta [mg/dL change/SD decrease in sclerostin levels]	0.01908919	0.03039105	0.52992621	<a href="https://csg.sph.umich.edu/willer/public/glgc-lipids2021/">https://csg.sph.umich.edu/willer/public/glgc-lipids2021/</a>
HDL cholesterol	2	Beta [mg/dL change/SD decrease in sclerostin levels]	-0.1455347	0.03013333	1.37E-06	<a href="https://csg.sph.umich.edu/willer/public/glgc-lipids2021/">https://csg.sph.umich.edu/willer/public/glgc-lipids2021/</a>
Fasting glucose	2	Beta [mmol/L change/SD decrease in sclerostin levels]	0.02641789	0.03965886	0.50532907	<a href="https://magicinvestigators.org/downloads/">https://magicinvestigators.org/downloads/</a>
HbA1c	2	Beta [% change/SD decrease in sclerostin levels]	0.02104062	0.02902738	0.46854154	<a href="https://magicinvestigators.org/downloads/">https://magicinvestigators.org/downloads/</a>
Coronary artery disease	2	OR / SD decrease in sclerostin levels	1.24958769	0.10954944	0.04196071	<a href="https://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST90132001-GCST90133000/GCST90132314/">https://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST90132001-GCST90133000/GCST90132314/</a>
Myocardial infarction	2	OR / SD decrease in sclerostin levels	1.35466428	0.16583496	0.06718173	<a href="https://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST011001-GCST012000/GCST011365/harmonised/">https://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST011001-GCST012000/GCST011365/harmonised/</a>
Ischaemic stroke	2	OR / SD decrease in sclerostin levels	1.18979215	0.15578975	0.2646495	<a href="https://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST90104001-GCST90105000/GCST90104540/">https://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST90104001-GCST90105000/GCST90104540/</a>
Hypertension	2	OR / SD decrease in sclerostin levels	1.0264745	0.01958368	0.18211216	ukb-b-14057
Type 2 diabetes mellitus	2	OR / SD decrease in sclerostin levels	1.44983479	0.1384198	0.00728558	<a href="https://www.ebi.ac.uk/gwas/studies/GCST90132184">https://www.ebi.ac.uk/gwas/studies/GCST90132184</a>

**Supplementary Table 5.** Study information of the UK Biobank cohorts.

<b>Outcome</b>	<b>Type of outcome</b>	<b>N</b>	<b>Age (SD)</b>	<b>Male (%)</b>	<b>Mean (SD) /Cases (%)</b>	<b>Mean followup</b>
Whole cohort	-	276,172	57 (8)	128,946 (47)	-	-
Cholesterol	Continuous	263,285	57 (8)	123,011 (47)	5.72 (1.14)	-
LDL cholesterol	Continuous	262,794	57 (8)	122,752 (47)	3.57 (0.87)	-
HDL cholesterol	Continuous	241,065	57 (8)	113,574 (47)	1.45 (0.38)	-
Triglycerides	Continuous	263,067	57 (8)	122,877 (47)	1.75 (1.02)	-
Apolipoprotein-A	Continuous	239,707	57 (8)	113,397 (47)	1.54 (0.27)	-
Apolipoprotein-B	Continuous	261,986	57 (8)	122,208 (47)	1.03 (0.24)	-
C-Reactive protein	Continuous	262,728	57 (8)	122,697 (47)	2.56 (4.35)	-
Lipoprotein (a)	Continuous	209,333	57 (8)	974,06 (47)	44.07 (49.44)	-
Glucose	Continuous	240,909	57 (8)	113,502 (47)	5.12 (1.21)	-
HbA1c	Continuous	263,079	57 (8)	122,845 (47)	35.92 (6.45)	-
Coronary artery disease	Binary	276,172	57 (8)	128,946 (47)	16,233 (6)	-
Myocardial infarction	Binary	276,172	57 (8)	128,946 (47)	10,861 (4)	-
Ischaemic stroke	Binary	276,172	57 (8)	128,946 (47)	3,830 (1)	-
Hypertension	Binary	276,172	57 (8)	128,946 (47)	98,040 (35)	-
Type 2 diabetes	Binary	276,172	57 (8)	128,946 (47)	21,664 (8)	-
Coronary artery disease	Survival	276,172	57 (8)	128,946 (47)	16,233 (6)	68 (8)
Myocardial infarction	Survival	276,065	57 (8)	128,876 (47)	10,754 (4)	68 (8)
Ischaemic stroke	Survival	276,172	57 (8)	128,946 (47)	3,830 (1)	68 (8)
Hypertension	Survival	271,359	57 (8)	127,354 (47)	93,227 (34)	63 (11)
Type 2 diabetes	Survival	266,268	57 (8)	122,592 (46)	11,760 (4)	68 (8)

**Supplementary Table 6.** Results of the Mendelian randomisation for UK Biobank outcomes.

Outcome	Instruments	Type of estimate	MR estimate	Standard error	P value
Cholesterol	2	Beta [SD change/SD decrease in sclerostin levels]	0.04351909	0.06003166	0.46849154
LDL cholesterol	2	Beta [SD change/SD decrease in sclerostin levels]	0.06030358	0.06081673	0.32141108
HDL cholesterol	2	Beta [SD change/SD decrease in sclerostin levels]	-0.1307288	0.05793801	0.02404829
Apolipoprotein-A	2	Beta [SD change/SD decrease in sclerostin levels]	-0.0782697	0.05897189	0.18443007
Apolipoprotein-B	2	Beta [SD change/SD decrease in sclerostin levels]	0.11891979	0.06111597	0.05167812
Lipoprotein (a)	2	Beta [SD change/SD decrease in sclerostin levels]	-0.0356529	0.06837771	0.60208033
C-Reactive protein	2	Beta [SD change/SD decrease in sclerostin levels]	0.01955029	0.06100932	0.7486291
Triglycerides	2	Beta [SD change/SD decrease in sclerostin levels]	0.26206403	0.05966256	1.12E-05
HbA1c	2	Beta [SD change/SD decrease in sclerostin levels]	-0.0045441	0.06088411	0.94050497
Glucose	2	Beta [SD change/SD decrease in sclerostin levels]	0.08939238	0.06360014	0.15986151
Coronary artery disease	2	OR / SD decrease in sclerostin levels	1.84897728	0.2572956	1.69E-02
Myocardial infarction	2	OR / SD decrease in sclerostin levels	1.37578563	0.31152161	0.30579464
Ischaemic stroke	2	OR / SD decrease in sclerostin levels	1.28494794	0.50747985	0.62127395
Hypertension	2	OR / SD decrease in sclerostin levels	1.18101945	0.13033265	0.20175612
Type 2 diabetes	2	OR / SD decrease in sclerostin levels	1.62002558	0.22238731	3.01E-02
Coronary artery disease	2	HR / SD decrease in sclerostin levels	1.770027	0.2437155	0.01913579
Myocardial infarction	2	HR / SD decrease in sclerostin levels	1.369607	0.30190278	0.29750167
Ischaemic stroke	2	HR / SD decrease in sclerostin levels	1.285523	0.50198067	0.6168292
Hypertension	2	HR / SD decrease in sclerostin levels	1.120222	0.10221314	0.26670209
Type 2 diabetes	2	HR / SD decrease in sclerostin levels	1.668812	0.28629863	0.07365778

**Supplementary Table 7.** Study information of the cohorts used for the GWAS meta-analysis of sclerostin.

Article reference	Study	Outcome	N	Age (SD)	% Female	Study population
Sun et al., 2018	INTERVAL study	Sclerostin	3,301	43 (14)	49	European (England)
Ferkingstad et al., 2021	deCODE genetics	Sclerostin	35,559	55 (17)	57	European (Iceland)
Pietzner et al., 2021	Fenland study	Sclerostin	10,708	49 (7)	53	European (England)

**Supplementary Table 8.** Study information of the cohorts used in the published GWAS summary statistic of the outcomes. Note: LDL cholesterol, HDL cholesterol, and HbA1c mean and standard values were not reported by the original publication and were estimated as weighted (by the sample sizes) average of the means reported in the contributing studies. Glucose mean value could not be estimated.

Article reference	Study	Outcome	N	Mean (SD)	Study population
				N cases (%)	
<b>Morris et al., 2019</b>	UK Biobank	Heel bone mineral density	426,824	0.54 (0.12) [g/cm <sup>2</sup> ]	European
<b>Nethander et al., 2022</b>	Meta-analysis	Hip fracture	735,354	11,516 (2)	European
<b>Aragam et al., 2022</b>	Meta-analysis	Coronary artery disease	1,165,690	181,522 (16)	European
<b>Hartiala et al., 2021</b>	Meta-analysis	Myocardial infarction	~639,000	~62,000 (10)	European
<b>Mishra et al., 2022</b>	Meta-analysis	Ischaemic stroke	1,847,683	612,875 (33)	European
<b>Elsworth et al., 2018</b>	UK Biobank	Hypertension	462,933	119,731 (26)	European
<b>Mahajan et al., 2022</b>	Meta-analysis	Type II diabetes mellitus	933,970	80,154 (9)	European
<b>Graham et al., 2021</b>	Meta-analysis	LDL-Cholesterol	1,228,508	131 [mg/dL]	European
<b>Graham et al., 2021</b>	Meta-analysis	HDL-Cholesterol	1,244,439	51.9 [mg/dL]	European
<b>Chen et al., 2021</b>	Meta-analysis	Fasting glucose	178,455	-	European
<b>Chen et al., 2021</b>	Meta-analysis	HbA1c	132,400	5.23 [mmol/l]	European



**Supplementary Table 9.** Sensitivity analyses results. Note: gIVW = generalised inverse variance weighted method, OR = Odds ratio, SD = Standard deviation, MR = Mendelian randomisation,.

Sensitivity analysis	Outcome	Source of outcome data	r <sup>2</sup> threshold	N instruments	N outcome	Type of MR estimate (units)	MR method	MR estimate	S.E of the MR estimate	P-Value of the MR estimate
Step-wise pruning	Heel bone mineral density	GWAS	r <sup>2</sup> ≤ 0.001	1	426,824	Beta [SD change/SD decrease in sclerostin levels]	Wald ratio	0.932381	0.04582019	4.77E-92
			r <sup>2</sup> ≤ 0.1	1	426,824	Beta [SD change/SD decrease in sclerostin levels]	gIVW	0.932381	0.04582019	4.77E-92
			r <sup>2</sup> ≤ 0.5	2	426,824	Beta [SD change/SD decrease in sclerostin levels]	gIVW	1.00187063	0.04024844	9.05E-137
			r <sup>2</sup> ≤ 0.8	6	426,824	Beta [SD change/SD decrease in sclerostin levels]	gIVW	0.53032519	0.19761409	0.00728254
Step-wise pruning	Hip fracture	GWAS	r <sup>2</sup> ≤ 0.001	1	735,354	OR / SD decrease in sclerostin levels	Wald ratio	0.18412271	0.35952255	2.52E-06
			r <sup>2</sup> ≤ 0.1	1	735,354	OR / SD decrease in sclerostin levels	gIVW	0.18412271	0.35952255	2.52E-06
			r <sup>2</sup> ≤ 0.5	2	735,354	OR / SD decrease in sclerostin levels	gIVW	0.15877783	0.330056	2.47E-08
			r <sup>2</sup> ≤ 0.8	6	735,354	OR / SD decrease in sclerostin levels	gIVW	0.37250533	0.39046181	0.01143663
Step-wise pruning	LDL cholesterol	GWAS	r <sup>2</sup> ≤ 0.001	1	1,228,508	Beta [mg/dL change/SD decrease in sclerostin levels]	Wald ratio	0.02570922	0.0342136	0.45239234
			r <sup>2</sup> ≤ 0.1	1	1,228,508	Beta [mg/dL change/SD decrease in sclerostin levels]	gIVW	0.02570922	0.0342136	0.45239234
			r <sup>2</sup> ≤ 0.5	2	1,228,508	Beta [mg/dL change/SD decrease in sclerostin levels]	gIVW	0.01908919	0.03039105	0.52992621
			r <sup>2</sup> ≤ 0.8	6	1,228,508	Beta [mg/dL change/SD decrease in sclerostin levels]	gIVW	-0.02232495	0.02297269	0.33114821
Step-wise pruning	HDL cholesterol	GWAS	r <sup>2</sup> ≤ 0.001	1	1,244,439	Beta [mg/dL change/SD decrease in sclerostin levels]	Wald ratio	-0.166144	0.0339128	9.63E-07
			r <sup>2</sup> ≤ 0.1	1	1,244,439	Beta [mg/dL change/SD decrease in sclerostin levels]	gIVW	-0.166144	0.0339128	9.63E-07
			r <sup>2</sup> ≤ 0.5	2	1,244,439	Beta [mg/dL change/SD decrease in sclerostin levels]	gIVW	-0.14553469	0.03013333	1.37E-06
			r <sup>2</sup> ≤ 0.8	6	1,244,439	Beta [mg/dL change/SD decrease in sclerostin levels]	gIVW	-0.15377985	0.08674871	0.07627765
Step-wise pruning	Fasting glucose	GWAS	r <sup>2</sup> ≤ 0.001	1	178,455	Beta [mmol/dL change/SD decrease in sclerostin levels]	Wald ratio	0	0.04314271	1
			r <sup>2</sup> ≤ 0.1	1	178,455	Beta [mmol/dL change/SD decrease in sclerostin levels]	gIVW	0	0.04314271	1
			r <sup>2</sup> ≤ 0.5	2	178,455	Beta [mmol/dL change/SD decrease in sclerostin levels]	gIVW	0.02641789	0.03965886	0.50532907
			r <sup>2</sup> ≤ 0.8	6	178,455	Beta [mmol/dL change/SD decrease in sclerostin levels]	gIVW	0.04282551	0.03192605	0.17979161

Step-wise pruning	HbA1c	GWAS	$r^2 \leq 0.001$	1	132,400	Beta [% change/SD decrease in sclerostin levels]	Wald ratio	0.02157135	0.03115862	0.48874412
			$r^2 \leq 0.1$	1	132,400	Beta [% change/SD decrease in sclerostin levels]	gIVW	0.02157135	0.03115862	0.48874412
			$r^2 \leq 0.5$	2	132,400	Beta [% change/SD decrease in sclerostin levels]	gIVW	0.02104062	0.02902738	0.46854154
			$r^2 \leq 0.8$	6	132,400	Beta [% change/SD decrease in sclerostin levels]	gIVW	0.00092934	0.02037851	0.96362612
Step-wise pruning	Coronary artery disease	GWAS	$r^2 \leq 0.001$	1	1,165,690	OR / SD decrease in sclerostin levels	Wald ratio	1.30240886	0.12446919	0.03377579
			$r^2 \leq 0.1$	1	1,165,690	OR / SD decrease in sclerostin levels	gIVW	1.30240886	0.12446919	0.03377579
			$r^2 \leq 0.5$	2	1,165,690	OR / SD decrease in sclerostin levels	gIVW	1.24958769	0.10954944	0.04196071
			$r^2 \leq 0.8$	6	1,165,690	OR / SD decrease in sclerostin levels	gIVW	1.05645197	0.09736719	0.57274715
Step-wise pruning	Myocardial infarction	GWAS	$r^2 \leq 0.001$	1	~639,000	OR / SD decrease in sclerostin levels	Wald ratio	1.28167323	0.18251762	0.17392968
			$r^2 \leq 0.1$	1	~639,000	OR / SD decrease in sclerostin levels	gIVW	1.28167323	0.18251762	0.17392968
			$r^2 \leq 0.5$	2	~639,000	OR / SD decrease in sclerostin levels	gIVW	1.35466428	0.16583496	0.06718173
			$r^2 \leq 0.8$	6	~639,000	OR / SD decrease in sclerostin levels	gIVW	1.21611639	0.10627912	0.06561792
Step-wise pruning	Ischaemic stroke	GWAS	$r^2 \leq 0.001$	1	1,847,683	OR / SD decrease in sclerostin levels	Wald ratio	1.32369569	0.17017401	0.0993758
			$r^2 \leq 0.1$	1	1,847,683	OR / SD decrease in sclerostin levels	gIVW	1.32369569	0.17017401	0.0993758
			$r^2 \leq 0.5$	2	1,847,683	OR / SD decrease in sclerostin levels	gIVW	1.18979215	0.15578975	0.2646495
			$r^2 \leq 0.8$	6	1,847,683	OR / SD decrease in sclerostin levels	gIVW	1.24937878	0.18716618	0.23421717
Step-wise pruning	Hypertension	GWAS	$r^2 \leq 0.001$	1	462,933	OR / SD decrease in sclerostin levels	Wald ratio	1.01383256	0.02224019	0.53677305
			$r^2 \leq 0.1$	1	462,933	OR / SD decrease in sclerostin levels	gIVW	1.01383256	0.02224019	0.53677305
			$r^2 \leq 0.5$	2	462,933	OR / SD decrease in sclerostin levels	gIVW	1.0264745	0.01958368	0.18211216
			$r^2 \leq 0.8$	6	462,933	OR / SD decrease in sclerostin levels	gIVW	1.00711378	0.0124633	0.56952081
Step-wise pruning	Type 2 diabetes	GWAS	$r^2 \leq 0.001$	1	933,970	OR / SD decrease in sclerostin levels	Wald ratio	1.56549925	0.15818992	0.00460653
			$r^2 \leq 0.1$	1	933,970	OR / SD decrease in sclerostin levels	gIVW	1.56549925	0.15818992	0.00460653
			$r^2 \leq 0.5$	2	933,970	OR / SD decrease in sclerostin levels	gIVW	1.44983479	0.1384198	0.00728559
			$r^2 \leq 0.8$	6	933,970	OR / SD decrease in sclerostin levels	gIVW	1.18970371	0.10298299	0.09165567
Step-wise pruning	Cholesterol	UK Biobank	$r^2 \leq 0.001$	1	263,285	Beta [SD change/SD decrease in sclerostin levels]	Wald ratio	0.04102183	0.06778907	0.54508646
			$r^2 \leq 0.1$	1	263,285	Beta [SD change/SD decrease in sclerostin levels]	gIVW	0.04102183	0.06778907	0.54508646
			$r^2 \leq 0.5$	2	263,285	Beta [SD change/SD decrease in sclerostin levels]	gIVW	0.04556569	0.05993822	0.4471285
			$r^2 \leq 0.8$	6	263,285	Beta [SD change/SD decrease in sclerostin levels]	gIVW	- 0.01860144	0.03810697	0.62545248
Step-wise pruning	LDL cholesterol	UK Biobank	$r^2 \leq 0.001$	1	262,794	Beta [SD change/SD decrease in sclerostin levels]	Wald ratio	0.05613282	0.06873121	0.41409954

			$r^2 \leq 0.1$	1	262,794	Beta [SD change/SD decrease in sclerostin levels]	gIVW	0.05613282	0.06873121	0.41409954
			$r^2 \leq 0.5$	2	262,794	Beta [SD change/SD decrease in sclerostin levels]	gIVW	0.06152508	0.06077499	0.31137453
			$r^2 \leq 0.8$	6	262,794	Beta [SD change/SD decrease in sclerostin levels]	gIVW	-0.0089142	0.03863295	0.81751619
Step-wise pruning	HDL cholesterol	UK Biobank	$r^2 \leq 0.001$	1	241,065	Beta [SD change/SD decrease in sclerostin levels]	Wald ratio	-0.14513568	0.06545376	0.02659731
			$r^2 \leq 0.1$	1	241,065	Beta [SD change/SD decrease in sclerostin levels]	gIVW	-0.14513568	0.06545376	0.02659731
			$r^2 \leq 0.5$	2	241,065	Beta [SD change/SD decrease in sclerostin levels]	gIVW	-0.12915149	0.05785454	0.02559196
			$r^2 \leq 0.8$	6	241,065	Beta [SD change/SD decrease in sclerostin levels]	gIVW	-0.14913587	0.0863536	0.08416102
Step-wise pruning	Triglycerides	UK Biobank	$r^2 \leq 0.001$	1	263,067	Beta [SD change/SD decrease in sclerostin levels]	Wald ratio	0.2810236	0.06733437	3.00E-05
			$r^2 \leq 0.1$	1	263,067	Beta [SD change/SD decrease in sclerostin levels]	gIVW	0.2810236	0.06733437	3.00E-05
			$r^2 \leq 0.5$	2	263,067	Beta [SD change/SD decrease in sclerostin levels]	gIVW	0.26412892	0.05955772	9.21E-06
			$r^2 \leq 0.8$	6	263,067	Beta [SD change/SD decrease in sclerostin levels]	gIVW	0.20606198	0.0788878	0.00899907
Step-wise pruning	Apolipoprotein-A	UK Biobank	$r^2 \leq 0.001$	1	239,707	Beta [SD change/SD decrease in sclerostin levels]	Wald ratio	-0.08536802	0.06636566	0.19832857
			$r^2 \leq 0.1$	1	239,707	Beta [SD change/SD decrease in sclerostin levels]	gIVW	-0.08536802	0.06636566	0.19832857
			$r^2 \leq 0.5$	2	239,707	Beta [SD change/SD decrease in sclerostin levels]	gIVW	-0.07523629	0.05865662	0.19961243
			$r^2 \leq 0.8$	6	239,707	Beta [SD change/SD decrease in sclerostin levels]	gIVW	-0.12005459	0.07950615	0.13104246
Step-wise pruning	Apolipoprotein-B	UK Biobank	$r^2 \leq 0.001$	1	261,986	Beta [SD change/SD decrease in sclerostin levels]	Wald ratio	0.10292112	0.06903513	0.13600051
			$r^2 \leq 0.1$	1	261,986	Beta [SD change/SD decrease in sclerostin levels]	gIVW	0.10292112	0.06903513	0.13600051
			$r^2 \leq 0.5$	2	261,986	Beta [SD change/SD decrease in sclerostin levels]	gIVW	0.12061292	0.06103368	0.04813554
			$r^2 \leq 0.8$	6	261,986	Beta [SD change/SD decrease in sclerostin levels]	gIVW	0.04324013	0.03880648	0.26517177
Step-wise pruning	C-Reactive protein	UK Biobank	$r^2 \leq 0.001$	1	262,728	Beta [SD change/SD decrease in sclerostin levels]	Wald ratio	2.95E-05	0.06887731	0.99965865
			$r^2 \leq 0.1$	1	262,728	Beta [SD change/SD decrease in sclerostin levels]	gIVW	2.95E-05	0.06887731	0.99965865
			$r^2 \leq 0.5$	2	262,728	Beta [SD change/SD decrease in sclerostin levels]	gIVW	0.02183399	0.06090094	0.71995686
			$r^2 \leq 0.8$	6	262,728	Beta [SD change/SD decrease in sclerostin levels]	gIVW	0.07297988	0.03880145	0.05999173
Step-wise pruning	Lipoprotein (a)	UK Biobank	$r^2 \leq 0.001$	1	209,333	Beta [SD change/SD decrease in sclerostin levels]	Wald ratio	-0.01551003	0.07731104	0.84099688

			$r^2 \leq 0.1$	1	209,333	Beta [SD change/SD decrease in sclerostin levels]	gIVW	-0.01551003	0.07731104	0.84099688
			$r^2 \leq 0.5$	2	209,333	Beta [SD change/SD decrease in sclerostin levels]	gIVW	-0.03528168	0.06837289	0.60584144
			$r^2 \leq 0.8$	6	209,333	Beta [SD change/SD decrease in sclerostin levels]	gIVW	0.02018616	0.05290314	0.70278158
Step-wise pruning	Glucose	UK Biobank	$r^2 \leq 0.001$	1	240,909	Beta [SD change/SD decrease in sclerostin levels]	Wald ratio	0.07511635	0.07157228	0.29394009
			$r^2 \leq 0.1$	1	240,909	Beta [SD change/SD decrease in sclerostin levels]	gIVW	0.07511635	0.07157228	0.29394009
			$r^2 \leq 0.5$	2	240,909	Beta [SD change/SD decrease in sclerostin levels]	gIVW	0.09284299	0.06323605	0.14205071
			$r^2 \leq 0.8$	6	240,909	Beta [SD change/SD decrease in sclerostin levels]	gIVW	0.05817519	0.04019481	0.14780427
Step-wise pruning	HbA1c	UK Biobank	$r^2 \leq 0.001$	1	263,079	Beta [SD change/SD decrease in sclerostin levels]	Wald ratio	-0.02147077	0.06735942	0.74991662
			$r^2 \leq 0.1$	1	263,079	Beta [SD change/SD decrease in sclerostin levels]	gIVW	-0.02147077	0.06735942	0.74991662
			$r^2 \leq 0.5$	2	263,079	Beta [SD change/SD decrease in sclerostin levels]	gIVW	0.00511291	0.05955887	0.93158865
			$r^2 \leq 0.8$	6	263,079	Beta [SD change/SD decrease in sclerostin levels]	gIVW	-0.00676307	0.03773946	0.85777749
Step-wise pruning	Coronary artery disease	UK Biobank (categorical)	$r^2 \leq 0.001$	1	276,172	OR / SD decrease in sclerostin levels	Wald ratio	1.90037182	0.29201352	0.0278994
			$r^2 \leq 0.1$	1	276,172	OR / SD decrease in sclerostin levels	gIVW	1.90037182	0.29201352	0.0278994
			$r^2 \leq 0.5$	2	276,172	OR / SD decrease in sclerostin levels	gIVW	1.84897728	0.2572956	0.01690262
			$r^2 \leq 0.8$	6	276,172	OR / SD decrease in sclerostin levels	gIVW	1.18382334	0.2135353	0.42937344
Step-wise pruning	Myocardial infarction	UK Biobank (categorical)	$r^2 \leq 0.001$	1	276,065	OR / SD decrease in sclerostin levels	Wald ratio	1.94938433	0.35089193	0.05712752
			$r^2 \leq 0.1$	1	276,065	OR / SD decrease in sclerostin levels	gIVW	1.94938433	0.35089193	0.05712752
			$r^2 \leq 0.5$	2	276,065	OR / SD decrease in sclerostin levels	gIVW	1.37578563	0.31152161	0.30579464
			$r^2 \leq 0.8$	6	276,065	OR / SD decrease in sclerostin levels	gIVW	1.05222933	0.27652222	0.85392552
Step-wise pruning	Ischaemic stroke	UK Biobank (categorical)	$r^2 \leq 0.001$	1	276,172	OR / SD decrease in sclerostin levels	Wald ratio	1.06633701	0.57773916	0.91147858
			$r^2 \leq 0.1$	1	276,172	OR / SD decrease in sclerostin levels	gIVW	1.06633701	0.57773916	0.91147858
			$r^2 \leq 0.5$	2	276,172	OR / SD decrease in sclerostin levels	gIVW	1.28494794	0.50747985	0.62127395
			$r^2 \leq 0.8$	6	276,172	OR / SD decrease in sclerostin levels	gIVW	0.76487017	0.4980223	0.59042017
Step-wise pruning	Hypertension	UK Biobank (categorical)	$r^2 \leq 0.001$	1	271,359	OR / SD decrease in sclerostin levels	Wald ratio	1.10875316	0.14752171	0.48405046
			$r^2 \leq 0.1$	1	271,359	OR / SD decrease in sclerostin levels	gIVW	1.10875316	0.14752171	0.48405046
			$r^2 \leq 0.5$	2	271,359	OR / SD decrease in sclerostin levels	gIVW	1.18101945	0.13033265	0.20175612
			$r^2 \leq 0.8$	6	271,359	OR / SD decrease in sclerostin levels	gIVW	1.05420031	0.08289579	0.52429883
			$r^2 \leq 0.001$	1	266,268	OR / SD decrease in sclerostin levels	Wald ratio	1.53819406	0.25258953	0.08823586

Step-wise pruning	Type 2 diabetes	UK Biobank (categorical)	$r^2 \leq 0.1$	1	266,268	OR / SD decrease in sclerostin levels	gIVW	1.53819406	0.25258953	0.08823586
			$r^2 \leq 0.5$	2	266,268	OR / SD decrease in sclerostin levels	gIVW	1.62002558	0.22238731	0.03005406
			$r^2 \leq 0.8$	6	266,268	OR / SD decrease in sclerostin levels	gIVW	1.45213146	0.14176496	0.00850478
Step-wise pruning	Coronary artery disease	UK Biobank (survival)	$r^2 \leq 0.001$	1	276,172	HR / SD decrease in sclerostin levels	Wald ratio	1.81289761	0.27670977	0.03155508
			$r^2 \leq 0.1$	1	276,172	HR / SD decrease in sclerostin levels	gIVW	1.81289761	0.27670977	0.03155508
			$r^2 \leq 0.5$	2	276,172	HR / SD decrease in sclerostin levels	gIVW	1.7700273	0.2437155	0.01913579
			$r^2 \leq 0.8$	6	276,172	HR / SD decrease in sclerostin levels	gIVW	1.16853246	0.20485376	0.44708013
Step-wise pruning	Myocardial infarction	UK Biobank (survival)	$r^2 \leq 0.001$	1	276,172	HR / SD decrease in sclerostin levels	Wald ratio	1.91498016	0.33999829	0.05601572
			$r^2 \leq 0.1$	1	276,172	HR / SD decrease in sclerostin levels	gIVW	1.91498016	0.33999829	0.05601572
			$r^2 \leq 0.5$	2	276,172	HR / SD decrease in sclerostin levels	gIVW	1.36960736	0.30190278	0.29750167
			$r^2 \leq 0.8$	6	276,172	HR / SD decrease in sclerostin levels	gIVW	1.04821662	0.27170394	0.86240413
Step-wise pruning	Ischaemic stroke	UK Biobank (survival)	$r^2 \leq 0.001$	1	276,172	HR / SD decrease in sclerostin levels	Wald ratio	1.05794812	0.57161586	0.92149758
			$r^2 \leq 0.1$	1	276,172	HR / SD decrease in sclerostin levels	gIVW	1.05794812	0.57161586	0.92149758
			$r^2 \leq 0.5$	2	276,172	HR / SD decrease in sclerostin levels	gIVW	1.285523	0.50198067	0.6168292
			$r^2 \leq 0.8$	6	276,172	HR / SD decrease in sclerostin levels	gIVW	0.77599628	0.49390784	0.6076216
Step-wise pruning	Hypertension	UK Biobank (survival)	$r^2 \leq 0.001$	1	276,172	HR / SD decrease in sclerostin levels	Wald ratio	1.07213831	0.11585293	0.5476821
			$r^2 \leq 0.1$	1	276,172	HR / SD decrease in sclerostin levels	gIVW	1.07213831	0.11585293	0.5476821
			$r^2 \leq 0.5$	2	276,172	HR / SD decrease in sclerostin levels	gIVW	1.12022218	0.10221314	0.26670209
			$r^2 \leq 0.8$	6	276,172	HR / SD decrease in sclerostin levels	gIVW	1.03596301	0.06504502	0.58700288
Step-wise pruning	Type 2 diabetes	UK Biobank (survival)	$r^2 \leq 0.001$	1	276,172	HR / SD decrease in sclerostin levels	Wald ratio	1.56900258	0.32568088	0.16664279
			$r^2 \leq 0.1$	1	276,172	HR / SD decrease in sclerostin levels	gIVW	1.56900258	0.32568088	0.16664279
			$r^2 \leq 0.5$	2	276,172	HR / SD decrease in sclerostin levels	gIVW	1.66881184	0.28629863	0.07365778
			$r^2 \leq 0.8$	6	276,172	HR / SD decrease in sclerostin levels	gIVW	1.65459767	0.18232995	0.00574846
Random-effects method	Heel bone mineral density	GWAS	$r^2 \leq 0.3$	1	426,824	Beta [SD change/SD decrease in sclerostin levels]	Wald ratio	1.12486981	0.0552528	3.90E-92
Random-effects method	Hip fracture	GWAS	$r^2 \leq 0.3$	1	735,354	OR [SD change/SD decrease in sclerostin levels]	Wald ratio	0.12116527	0.4270796	7.74E-07
Random-effects method	LDL cholesterol	GWAS	$r^2 \leq 0.3$	1	1,228,508	Beta [mg/dL change/SD decrease in sclerostin levels]	Wald ratio	0.01730604	0.04112336	0.67387754
Random-effects method	HDL cholesterol	GWAS	$r^2 \leq 0.3$	1	1,244,439	Beta [mg/dL change/SD decrease in sclerostin levels]	Wald ratio	-0.30898245	0.04076048	3.44E-14

Random-effects method	Fasting glucose	GWAS	$r^2 \leq 0.3$	1	178,455	Beta [mmol/L change/SD decrease in sclerostin levels]	Wald ratio	-0.01102141	0.05235169	0.83325692
Random-effects method	HbA1c	GWAS	$r^2 \leq 0.3$	1	132,400	Beta [% change/SD decrease in sclerostin levels]	Wald ratio	0.01928747	0.03857493	0.61707508
Random-effects method	Coronary artery disease	GWAS	$r^2 \leq 0.3$	1	1,165,690	OR [SD change/SD decrease in sclerostin levels]	Wald ratio	1.50850935	0.1456142	0.00475225
Random-effects method	Myocardial infarction	GWAS	$r^2 \leq 0.3$	1	~639,000	OR [SD change/SD decrease in sclerostin levels]	Wald ratio	1.4619486	0.22020775	0.08459966
Random-effects method	Ischaemic stroke	GWAS	$r^2 \leq 0.3$	1	1,847,683	OR [SD change/SD decrease in sclerostin levels]	Wald ratio	1.11038121	0.20114072	0.60268172
Random-effects method	Hypertension	GWAS	$r^2 \leq 0.3$	1	462,933	OR [SD change/SD decrease in sclerostin levels]	Wald ratio	1.03209637	0.02681732	0.23877818
Random-effects method	Type 2 diabetes	GWAS	$r^2 \leq 0.3$	1	933,970	OR [SD change/SD decrease in sclerostin levels]	Wald ratio	1.81831717	0.18736395	0.00141695
Random-effects method	Cholesterol	UK Biobank	$r^2 \leq 0.3$	1	263,285	Beta [SD change/SD decrease in sclerostin levels]	Wald ratio	0.03712163	0.08183082	0.65008887
Random-effects method	LDL cholesterol	UK Biobank	$r^2 \leq 0.3$	1	262,794	Beta [SD change/SD decrease in sclerostin levels]	Wald ratio	0.07041799	0.08297635	0.39607537
Random-effects method	HDL cholesterol	UK Biobank	$r^2 \leq 0.3$	1	241,065	Beta [SD change/SD decrease in sclerostin levels]	Wald ratio	-0.30712607	0.07900578	0.00010133
Random-effects method	Triglycerides	UK Biobank	$r^2 \leq 0.3$	1	263,067	Beta [SD change/SD decrease in sclerostin levels]	Wald ratio	0.45840662	0.08130907	1.72E-08
Random-effects method	Apolipoprotein-A	UK Biobank	$r^2 \leq 0.3$	1	239,707	Beta [SD change/SD decrease in sclerostin levels]	Wald ratio	-0.22392764	0.08010977	0.0051858
Random-effects method	Apolipoprotein-B	UK Biobank	$r^2 \leq 0.3$	1	261,986	Beta [SD change/SD decrease in sclerostin levels]	Wald ratio	0.15026865	0.08333518	0.07135937
Random-effects method	C-Reactive protein	UK Biobank	$r^2 \leq 0.3$	1	262,728	Beta [SD change/SD decrease in sclerostin levels]	Wald ratio	0.04158791	0.0831949	0.61715578
Random-effects method	Lipoprotein (a)	UK Biobank	$r^2 \leq 0.3$	1	209,333	Beta [SD change/SD decrease in sclerostin levels]	Wald ratio	-0.03791987	0.09336314	0.684629

Random-effects method	Glucose	UK Biobank	$r^2 \leq 0.3$	1	240,909	Beta [SD change/SD decrease in sclerostin levels]	Wald ratio	0.065245	0.086256	0.44940274
Random-effects method	HbA1c	UK Biobank	$r^2 \leq 0.3$	1	263,079	Beta [SD change/SD decrease in sclerostin levels]	Wald ratio	0.00577451	0.08129073	0.94336968
Random-effects method	Coronary artery disease	UK Biobank (categorical)	$r^2 \leq 0.3$	1	276,172	OR [SD change/SD decrease in sclerostin levels]	Wald ratio	2.72020211	0.35153142	0.00441743
Random-effects method	Myocardial infarction	UK Biobank (categorical)	$r^2 \leq 0.3$	1	276,065	OR [SD change/SD decrease in sclerostin levels]	Wald ratio	2.66706624	0.42266155	0.02028919
Random-effects method	Ischaemic stroke	UK Biobank (categorical)	$r^2 \leq 0.3$	1	276,172	OR [SD change/SD decrease in sclerostin levels]	Wald ratio	2.93811502	0.69288847	0.11983383
Random-effects method	Hypertension	UK Biobank (categorical)	$r^2 \leq 0.3$	1	271,359	OR [SD change/SD decrease in sclerostin levels]	Wald ratio	1.2325754	0.1780945	0.24034363
Random-effects method	Type 2 diabetes	UK Biobank (categorical)	$r^2 \leq 0.3$	1	266,268	OR [SD change/SD decrease in sclerostin levels]	Wald ratio	1.50858669	0.30488516	0.17746009
Random-effects method	Coronary artery disease	UK Biobank (survival)	$r^2 \leq 0.3$	1	276,172	HR [SD change/SD decrease in sclerostin levels]	Wald ratio	2.58383609	0.33310728	0.00437525
Random-effects method	Myocardial infarction	UK Biobank (survival)	$r^2 \leq 0.3$	1	276,172	HR [SD change/SD decrease in sclerostin levels]	Wald ratio	2.61652135	0.40944941	0.01881785
Random-effects method	Ischaemic stroke	UK Biobank (survival)	$r^2 \leq 0.3$	1	276,172	HR [SD change/SD decrease in sclerostin levels]	Wald ratio	2.89519075	0.68559593	0.12100948
Random-effects method	Hypertension	UK Biobank (survival)	$r^2 \leq 0.3$	1	276,172	HR [SD change/SD decrease in sclerostin levels]	Wald ratio	1.18803669	0.13987401	0.21800965
Random-effects method	Type 2 diabetes	UK Biobank (survival)	$r^2 \leq 0.3$	1	276,172	HR [SD change/SD decrease in sclerostin levels]	Wald ratio	1.42239061	0.39325945	0.37028194
Principal components analysis	Heel bone mineral density	GWAS	$r^2 \leq 0.3$	76	426,824	Beta [SD change/SD decrease in sclerostin levels]	IVW	0.94154294	0.03766465	2.07E-121
Principal components analysis	Hip fracture	GWAS	$r^2 \leq 0.3$	76	735,354	OR [SD change/SD decrease in sclerostin levels]	IVW	0.19890407	0.29719333	9.40E-08

Principal components analysis	LDL cholesterol	GWAS	$r^2 \leq 0.3$	76	1,228,508	Beta [mg/dL change/SD decrease in sclerostin levels]	IVW	0.00208898	0.02869987	0.94706043
Principal components analysis	HDL cholesterol	GWAS	$r^2 \leq 0.3$	76	1,244,439	Beta [mg/dL change/SD decrease in sclerostin levels]	IVW	-0.11481814	0.02847307	6.40E-05
Principal components analysis	Fasting glucose	GWAS	$r^2 \leq 0.3$	76	178,455	Beta [mmol/L change/SD decrease in sclerostin levels]	IVW	0.03867948	0.03779884	0.31057976
Principal components analysis	HbA1c	GWAS	$r^2 \leq 0.3$	76	132,400	Beta [% change/SD decrease in sclerostin levels]	IVW	0.01175036	0.02868469	0.6952268
Principal components analysis	Coronary artery disease	GWAS	$r^2 \leq 0.3$	76	1,165,690	OR [SD change/SD decrease in sclerostin levels]	IVW	1.20602835	0.10233798	0.06677434
Principal components analysis	Myocardial infarction	GWAS	$r^2 \leq 0.3$	76	~639,000	OR [SD change/SD decrease in sclerostin levels]	IVW	1.30150483	0.15644801	0.09181376
Principal components analysis	Ischaemic stroke	GWAS	$r^2 \leq 0.3$	76	1,847,683	OR [SD change/SD decrease in sclerostin levels]	IVW	1.15602434	0.14550135	0.32383292
Principal components analysis	Hypertension	GWAS	$r^2 \leq 0.3$	76	462,933	OR [SD change/SD decrease in sclerostin levels]	IVW	1.02140871	0.01837844	0.25181914
Principal components analysis	Type 2 diabetes	GWAS	$r^2 \leq 0.3$	76	933,970	OR [SD change/SD decrease in sclerostin levels]	IVW	1.42863957	0.13029785	0.00621373
Survival analysis since UK Biobank enrolment	Coronary artery disease	UK Biobank (survival)	$r^2 \leq 0.3$	2	276,172	HR [SD change/SD decrease in sclerostin levels]	gIVW	1.82073661	0.29815486	0.04444898
Survival analysis since UK Biobank enrolment	Myocardial infarction	UK Biobank (survival)	$r^2 \leq 0.3$	2	276,172	HR [SD change/SD decrease in sclerostin levels]	gIVW	1.32316048	0.46505493	0.5470881
Survival analysis since UK Biobank enrolment	Ischaemic stroke	UK Biobank (survival)	$r^2 \leq 0.3$	2	276,172	HR [SD change/SD decrease in sclerostin levels]	gIVW	1.05959671	0.5518593	0.91645755
Survival analysis since UK Biobank enrolment	Hypertension	UK Biobank (survival)	$r^2 \leq 0.3$	2	276,172	HR [SD change/SD decrease in sclerostin levels]	gIVW	1.2575155	0.20022176	0.25244917
Survival analysis since UK Biobank enrolment	Type 2 diabetes	UK Biobank (survival)	$r^2 \leq 0.3$	2	276,172	HR [SD change/SD decrease in sclerostin levels]	gIVW	1.95012545	0.37133237	0.07207546



**Supplementary Table 10.** Phenotyping codes used for UK Biobank outcomes.

Continuous outcomes						
Source data: UK Biobank						
Field	Code	Description	Extra information	As continuous outcome		
3148.0.0		Heel bone mineral density (BMD)		Standardized to SD Value		
30690.0.0		Cholesterol		Standardized to SD Value		
30780.0.0		LDL direct		Standardized to SD Value		
30760.0.0		HDL cholesterol		Standardized to SD Valud		
30870.0.0		Triglycerides		Standardized to SD Value		
30630.0.0		Apolipoprotein A		Standardized to SD Value		
30640.0.0		Apolipoprotein B		Standardized to SD Value		
30710.0.0		C-Reactive protein		Standardized to SD Value		
30790.0.0		Lipoprotein A		Standardized to SD Value		
30750.0.0		Glycated haemoglobin (HbA1c)		Standardized to SD Value		
30740.0.0		Glucose		Standardized to SD Value		
Fracture risk outcome						
Source data: UK Biobank						
Field	Code	Description	Extra information	As binary utcome	As survival outcome (since birth date)	As survival outcome (since enrolment date)
3005		Fracture resulting from simple fall (from the last five years)		Patient included	Patient included, date of the event is the UK Biobank recruitment date (Field 53)	Patient excluded
20002	1632	fracture shoulder / scapula		Patient included	Patient included, years at the event is Field 20009 (Interpolated year/age of the event)	Patient excluded
20002	1633	fracture upper arm / humerus / elbow		Patient included	Patient included, years at the event is Field 20009 (Interpolated year/age of the event)	Patient excluded
20002	1634	fracture forearm / wrist		Patient included	Patient included, years at the event is Field 20009 (Interpolated year/age of the event)	Patient excluded
20002	1635	fracture radius		Patient included	Patient included, years at the event is Field 20009 (Interpolated year/age of the event)	Patient excluded
20002	1637	fracture wrist / colles fracture		Patient included	Patient included, years at the event is Field 20009 (Interpolated year/age of the event)	Patient excluded
20002	1644	fracture rib		Patient included	Patient included, years at the event is Field 20009 (Interpolated year/age of the event)	Patient excluded
20002	1646	fracture vertebra / crush fracture / vertebral collapse		Patient included	Patient included, years at the event is Field 20009 (Interpolated year/age of the event)	Patient excluded
20002	1647	fracture pelvis		Patient included	Patient included, years at the event is Field 20009 (Interpolated year/age of the event)	Patient excluded
20002	1648	fracture neck of femur / hip		Patient included	Patient included, years at the event is Field 20009 (Interpolated year/age of the event)	Patient excluded
Source data: Linkage to HES						
ICD-10	Code	Description	Extra information	As binary utcome	As survival outcome (since birth date)	As survival outcome (since enrolment date)
S720		Fracture of neck of femur		Patient included	Patient included, date of the event is the minimum between "epistart" and "admidate"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is the minimum between "epistart" and "admidate"
S721		Pertrochanteric fracture		Patient included	Patient included, date of the event is the minimum between "epistart" and "admidate"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is the minimum between "epistart" and "admidate"
S729		Fracture of femur, part unspecified		Patient included	Patient included, date of the event is the minimum between "epistart" and "admidate"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is the minimum between "epistart" and "admidate"
S722		Subtrochanteric fracture		Patient included	Patient included, date of the event is the minimum between "epistart" and "admidate"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is the minimum between "epistart" and "admidate"
S327		Multiple fractures of lumbar spine and pelvis		Patient included	Patient included, date of the event is the minimum between "epistart" and "admidate"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is the minimum between "epistart" and "admidate"
S321		Fracture of sacrum		Patient included	Patient included, date of the event is the minimum between "epistart" and "admidate"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is the minimum between "epistart" and "admidate"

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S529		Fracture of forearm, part unspecified		Patient included	Patient included, date of the event is the minimum between "epistart" and "admidate"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is the minimum between "epistart" and "admidate"
<b>Source data: Linkage to GP</b>						
<b>Read2 code</b>	<b>Code</b>	<b>Description</b>	<b>Extra information</b>	<b>As binary outcome</b>	<b>As survival outcome (since birth date)</b>	<b>As survival outcome (since enrolment date)</b>
7K1D0		Primary open reduction and internal fixation of proximal femoral fracture with screw/nail and plate device		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
7K1DE		Primary open reduction of fracture of neck of femur and open fixation using proximal femoral nail antirotation		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
7K1E6		Primary open reduction of fracture of elbow and fixation with Hook fixation plate		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
7K1J0		Closed reduction and internal fixation of proximal femoral fracture with screw/nail device alone		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
7K1Jd		Closed reduction of intracapsular fracture of neck of femur and internal fixation using a dynamic hip screw		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
7K1L4		Closed reduction of fracture of hip		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
7K1L5		Closed reduction of fracture of femur		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
7K1LE		Closed reduction of fracture of elbow		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
7K1LF		Closed reduction of fracture of humerus		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
7K1LG		Closed reduction of fracture of shoulder		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
7K1LL		Closed reduction of fracture of radius and or ulna		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
7K1LM		Closed reduction of fracture of wrist		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
N1y1.		Fatigue fracture of vertebra		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
N3310		Pathological fracture of thoracic vertebra		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
N3311		Pathological fracture of lumbar vertebra		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
N3318		Osteoporosis + pathological fracture lumbar vertebrae		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
N3319		Osteoporosis + pathological fracture thoracic vertebrae		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
S102.		Closed fracture thoracic vertebra		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
S1020		Closed fracture thoracic vertebra, burst		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
S1021		Closed fracture thoracic vertebra, wedge		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
S1022		Closed fracture thoracic vertebra, spondylolysis		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
S102y		Other specified closed fracture thoracic vertebra		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
S102z		Closed fracture thoracic vertebra not otherwise specified		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
S104.		Closed fracture lumbar vertebra		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
S1040		Closed fracture lumbar vertebra, burst		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"

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[illegible]

S2351		Open Colles' fracture		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
<b>Coronary artery disease outcome</b>						
<i>Source data: Linkage to HES</i>						
ICD10	Code	Description	Extra information	As binary outcome	As survival outcome (since birth date)	As survival outcome (since enrolment date)
I251		Atherosclerotic heart disease		Patient included	Patient included, date of the event is the Minimum between "epistart" and "admidate"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is the minimum between "epistart" and "admidate".
<i>Source data: Linkage to GP</i>						
Read2 code	Code	Description	Extra information	As binary outcome	As survival outcome (since birth date)	As survival outcome (since enrolment date)
G340.		Coronary atherosclerosis		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
G3400		Single coronary vessel disease		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
G3401		Double coronary vessel disease		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
G704.		Non-obstructive coronary atherosclerosis		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
<b>Myocardial infarction outcome</b>						
<i>Source data: UK Biobank</i>						
Field	Code	Description	Extra information	As binary outcome	As survival outcome (since birth date)	As survival outcome (since enrolment date)
3894		Age heart attack diagnosed		Patient included	Patient included, years at the event is provided by the same field	Patient excluded
20002	1075	Non-cancer illness code, self-reported - Heart attack/Myocardial infarction		Patient included	Patient included, years at the event is Field 20009 (Interpolated year/age of the event)	Patient excluded
<i>Source data: Linkage to HES</i>						
ICD10	Code	Description	Extra information	As binary outcome	As survival outcome (since birth date)	As survival outcome (since enrolment date)
I21		Acute myocardial infarction		Patient included	Patient included, date of the event is the minimum between "epistart" and "admidate"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is the minimum between "epistart" and "admidate"
I210		Acute transmural myocardial infarction of anterior wall		Patient included	Patient included, date of the event is the minimum between "epistart" and "admidate"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is the minimum between "epistart" and "admidate"
I211		Acute transmural myocardial infarction of inferior wall		Patient included	Patient included, date of the event is the minimum between "epistart" and "admidate"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is the minimum between "epistart" and "admidate"
I212		Acute transmural myocardial infarction of other sites		Patient included	Patient included, date of the event is the minimum between "epistart" and "admidate"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is the minimum between "epistart" and "admidate"
I213		Acute transmural myocardial infarction of unspecified site		Patient included	Patient included, date of the event is the minimum between "epistart" and "admidate"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is the minimum between "epistart" and "admidate"
I214		Acute subendocardial myocardial infarction		Patient included	Patient included, date of the event is the minimum between "epistart" and "admidate"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is the minimum between "epistart" and "admidate"
I219		Acute myocardial infarction, unspecified		Patient included	Patient included, date of the event is the minimum between "epistart" and "admidate"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is the minimum between "epistart" and "admidate"
I22		Subsequent myocardial infarction		Patient included	Patient included, date of the event is the minimum between "epistart" and "admidate"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is the minimum between "epistart" and "admidate"
I220		Subsequent myocardial infarction of anterior wall		Patient included	Patient included, date of the event is the minimum between "epistart" and "admidate"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is the minimum between "epistart" and "admidate"
I221		Subsequent myocardial infarction of inferior wall		Patient included	Patient included, date of the event is the minimum between "epistart" and "admidate"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is the minimum between "epistart" and "admidate"
I228		Subsequent myocardial infarction of other sites		Patient included	Patient included, date of the event is the minimum between "epistart" and "admidate"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is the minimum between "epistart" and "admidate"

I229		Subsequent myocardial infarction of unspecified site		Patient included	Patient included, date of the event is the minimum between "epistart" and "admidate"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is the minimum between "epistart" and "admidate"
I23		Certain current complications following acute myocardial infarction		Patient included	Patient included, date of the event is the minimum between "epistart" and "admidate"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is the minimum between "epistart" and "admidate"
I230		Haemopericardium as current complication following acute myocardial infarction		Patient included	Patient included, date of the event is the minimum between "epistart" and "admidate"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is the minimum between "epistart" and "admidate"
I231		Atrial septal defect as current complication following acute myocardial infarction		Patient included	Patient included, date of the event is the minimum between "epistart" and "admidate"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is the minimum between "epistart" and "admidate"
I232		Ventricular septal defect as current complication following acute myocardial infarction		Patient included	Patient included, date of the event is the minimum between "epistart" and "admidate"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is the minimum between "epistart" and "admidate"
I233		Rupture of cardiac wall without haemopericardium as current complication following acute myocardial infarction		Patient included	Patient included, date of the event is the minimum between "epistart" and "admidate"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is the minimum between "epistart" and "admidate"
I234		Rupture of chordae tendineae as current complication following acute myocardial infarction		Patient included	Patient included, date of the event is the minimum between "epistart" and "admidate"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is the minimum between "epistart" and "admidate"
I235		Rupture of papillary muscle as current complication following acute myocardial infarction		Patient included	Patient included, date of the event is the minimum between "epistart" and "admidate"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is the minimum between "epistart" and "admidate"
I236		Thrombosis of atrium, auricular appendage, and ventricle as current complications following acute myocardial infarction		Patient included	Patient included, date of the event is the minimum between "epistart" and "admidate"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is the minimum between "epistart" and "admidate"
I238		Other current complications following acute myocardial infarction		Patient included	Patient included, date of the event is the minimum between "epistart" and "admidate"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is the minimum between "epistart" and "admidate"
<b>Source data: Linkage to GP</b>						
<b>Read2 code</b>	<b>Code</b>	<b>Description</b>	<b>Extra information</b>	<b>As binary outcome</b>	<b>As survival outcome (since birth date)</b>	<b>As survival outcome (since enrolment date)</b>
G300.		Acute anterolateral infarction		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
G301.		Other specified anterior myocardial infarction		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
G3010		Acute anteroapical infarction		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
G3011		Acute anteroseptal infarction		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
G301z		Anterior myocardial infarction NOS		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
G302.		Acute inferolateral infarction		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
G303.		Acute inferoposterior infarction		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
G304.		Posterior myocardial infarction NOS		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
G305.		Lateral myocardial infarction NOS		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
G306.		True posterior myocardial infarction		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
G307.		Acute subendocardial infarction		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
G3070		Acute non-Q wave infarction		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
G3071		Acute non-ST segment elevation myocardial infarction		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"

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G380.		Postoperative transmural myocardial infarction of anterior wall		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
G381.		Postoperative transmural myocardial infarction of inferior wall		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
G382.		Postoperative transmural myocardial infarction of other sites		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
G383.		Postoperative transmural myocardial infarction of unspecified site		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
G384.		Postoperative subendocardial myocardial infarction		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
G38z.		Postoperative myocardial infarction, unspecified		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
G501.		Post infarction pericarditis		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
Gyu31		[X]Other current complications following acute myocardial infarction		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
Gyu34		[X]Acute transmural myocardial infarction of unspecified site		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
Gyu35		[X]Subsequent myocardial infarction of other sites		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
Gyu36		[X]Subsequent myocardial infarction of unspecified site		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"

## Ischaemic stroke outcome

Source data: UK Biobank

Field	Code	Description	Extra information	As binary outcome	As survival outcome (since birth date)	As survival outcome (since enrolment date)
20002	1583	Ischaemic stroke		Patient included	Patient included, years at the event is provided by Field 20009 (Interpolated year/age of the event)	Patient excluded

*Source data: Linkage to HES*

ICD10	Code	Description	Extra information	As binary outcome	As survival outcome (since birth date)	As survival outcome (since enrolment date)
I63		I63 Cerebral infarction		Patient included	Patient included, date of the event is the minimum between "epistart" and "admidate"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is the minimum between "epistart" and "admidate"
I630		I63.0 Cerebral infarction due to thrombosis of precerebral arteries		Patient included	Patient included, date of the event is the minimum between "epistart" and "admidate"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is the minimum between "epistart" and "admidate"
I631		I63.1 Cerebral infarction due to embolism of precerebral arteries		Patient included	Patient included, date of the event is the minimum between "epistart" and "admidate"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is the minimum between "epistart" and "admidate"
I632		I63.2 Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries		Patient included	Patient included, date of the event is the minimum between "epistart" and "admidate"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is the minimum between "epistart" and "admidate"
I633		I63.3 Cerebral infarction due to thrombosis of cerebral arteries		Patient included	Patient included, date of the event is the minimum between "epistart" and "admidate"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is the minimum between "epistart" and "admidate"
I634		I63.4 Cerebral infarction due to embolism of cerebral arteries		Patient included	Patient included, date of the event is the minimum between "epistart" and "admidate"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is the minimum between "epistart" and "admidate"
I635		I63.5 Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries		Patient included	Patient included, date of the event is the minimum between "epistart" and "admidate"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is the minimum between "epistart" and "admidate"
I636		I63.6 Cerebral infarction due to cerebral venous thrombosis, nonpyogenic		Patient included	Patient included, date of the event is the minimum between "epistart" and "admidate"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is the minimum between "epistart" and "admidate"
I638		I63.8 Other cerebral infarction		Patient included	Patient included, date of the event is the minimum between "epistart" and "admidate"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is the minimum between "epistart" and "admidate"
I639		I63.9 Cerebral infarction, unspecified		Patient included	Patient included, date of the event is the minimum between "epistart" and "admidate"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is the minimum between "epistart" and "admidate"

*Source data: Linkage to GP*

Read2 code	Code	Description	Extra information	As binary outcome	As survival outcome (since birth date)	As survival outcome (since enrolment date)
G63y0		Cerebral infarct due to thrombosis of precerebral arteries		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
G63y1		Cerebral infarction due to embolism of precerebral arteries		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
G6400		Cerebral infarction due to thrombosis of cerebral arteries		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
G6410		Cerebral infarction due to embolism of cerebral arteries		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
G64z.		Cerebral infarction NOS		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
G64z0		Brainstem infarction		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
G64z2		Left sided cerebral infarction		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
G64z3		Right sided cerebral infarction		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
G64z4		Infarction of basal ganglia		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
G6760		Cerebral infarction due to cerebral venous thrombosis, nonpyogenic		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
G6W..		Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
G6X..		Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
Gyu63		[X]Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
Gyu64		[X]Other cerebral infarction		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
Gyu6G		[X]Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries		Patient included	Patient included, date of the event is "event_dt"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is "event_dt"
<b>Hypertension outcome</b>						
<b>Source data: UK Biobank</b>						
Field	Code	Description	Extra information	As binary outcome	As survival outcome (since birth date)	As survival outcome (since enrolment date)
20002	1065	Non-cancer illness code, self-reported - Hypertension		Patient included	Patient included, years at the event is Field 20009 (Interpolated year/age of the event)	Patient excluded
<b>Source data: Linkage to HES</b>						
ICD10	Code	Description	Extra information	As binary outcome	As survival outcome (since birth date)	As survival outcome (since enrolment date)
I10		Essential (primary) hypertension		Patient included	Patient included, date of the event is the minimum between "epistart" and "admidate"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is the minimum between "epistart" and "admidate"
I11		Hypertensive heart disease		Patient included	Patient included, date of the event is the minimum between "epistart" and "admidate"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is the minimum between "epistart" and "admidate"
I110		Hypertensive heart disease with (congestive) heart failure		Patient included	Patient included, date of the event is the minimum between "epistart" and "admidate"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is the minimum between "epistart" and "admidate"
I119		Hypertensive heart disease without (congestive) heart failure		Patient included	Patient included, date of the event is the minimum between "epistart" and "admidate"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is the minimum between "epistart" and "admidate"
I12		Hypertensive renal disease		Patient included	Patient included, date of the event is the minimum between "epistart" and "admidate"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is the minimum between "epistart" and "admidate"
I120		Hypertensive renal disease with renal failure		Patient included	Patient included, date of the event is the minimum between "epistart" and "admidate"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is the minimum between "epistart" and "admidate"
I129		Hypertensive renal disease without renal failure		Patient included	Patient included, date of the event is the minimum between "epistart" and "admidate"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is the minimum between "epistart" and "admidate"

[illegible]



[illegible]

Field	Code	Description	Extra information	As binary outcome	As survival outcome (since birth date)	As survival outcome (since enrolment date)
2443		Diabetes diagnosed by a doctor		Patient included	Patient included, years at the event is provided by Field 2976 (Age diabetes diagnosed)	Patient excluded
20002	1223	Non-cancer illness code, self-reported - Type 2 diabetes		Patient included	Patient included, years at the event is provided by field 20009 (Interpolated year/age of the event)	Patient excluded
20003	1140874646	Glipizide		Patient included	Patient excluded	Patient excluded
20003	1140874664	Tolazamide		Patient included	Patient excluded	Patient excluded
20003	1140874674	Tolbutamide		Patient included	Patient excluded	Patient excluded
20003	1140874686	Glucophage		Patient included	Patient excluded	Patient excluded
20003	1140874706	Chlorpropamide)		Patient included	Patient excluded	Patient excluded
20003	1140874718	Glibenclamide		Patient included	Patient excluded	Patient excluded
20003	1140874744	Gliclazide		Patient included	Patient excluded	Patient excluded
20003	1141189090	Rosiglitazone/Metformin		Patient included	Patient excluded	Patient excluded
20003	1141171646	Pioglitazone		Patient included	Patient excluded	Patient excluded
20003	1140868902	Acarbose		Patient included	Patient excluded	Patient excluded
20003	1141168660	Repaglinide		Patient included	Patient excluded	Patient excluded
20003	1141152590	Glimepiride		Patient included	Patient excluded	Patient excluded
20003	1140874650	Glibenese		Patient included	Patient excluded	Patient excluded
20003	1140874652	Minodiab		Patient included	Patient excluded	Patient excluded
20003	1140874658	Gliquidone		Patient included	Patient excluded	Patient excluded
20003	1140874660	Glurenorm		Patient included	Patient excluded	Patient excluded
20003	1140874666	Tolanase		Patient included	Patient excluded	Patient excluded
20003	1140874678	Glyconon		Patient included	Patient excluded	Patient excluded
20003	1140874680	Rastinon		Patient included	Patient excluded	Patient excluded
20003	1140874690	Orabet		Patient included	Patient excluded	Patient excluded
20003	1140874712	Diabinese		Patient included	Patient excluded	Patient excluded
20003	1140874716	Glymese		Patient included	Patient excluded	Patient excluded
20003	1140874724	Daonil		Patient included	Patient excluded	Patient excluded
20003	1140874726	Semi-Daonil		Patient included	Patient excluded	Patient excluded
20003	1140874728	Euglucon		Patient included	Patient excluded	Patient excluded
20003	1140874732	Malix		Patient included	Patient excluded	Patient excluded
20003	1140874736	Diabetamide		Patient included	Patient excluded	Patient excluded
20003	1140874740	Calabren		Patient included	Patient excluded	Patient excluded
20003	1140874746	Diamicron		Patient included	Patient excluded	Patient excluded
20003	1141171652	Actos		Patient included	Patient excluded	Patient excluded
20003	1140868908	Glucobay		Patient included	Patient excluded	Patient excluded
20003	1141168668	Novonorm		Patient included	Patient excluded	Patient excluded
20003	1141157284	Glipizide product		Patient included	Patient excluded	Patient excluded
30750	HbA1c	HbA1c greater than 48 mmol/mol is diagnosed as diabetes		Patient included	Patient excluded	Patient excluded

**Source data: Linkage to HES**

ICD10	Code	Description	Extra information	As binary outcome	As survival outcome (since birth date)	As survival outcome (since enrolment date)
E11		Non-insulin-dependent diabetes mellitus		Patients included	Patient included, date of the event is the minimum between "epistart" and "admidate"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is the minimum between "epistart" and "admidate"
E110		With coma		Patients included	Patient included, date of the event is the minimum between "epistart" and "admidate"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is the minimum between "epistart" and "admidate"
E111		With ketoacidosis		Patients included	Patient included, date of the event is the minimum between "epistart" and "admidate"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is the minimum between "epistart" and "admidate"
E112		With renal complications		Patients included	Patient included, date of the event is the minimum between "epistart" and "admidate"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is the minimum between "epistart" and "admidate"
E113		With ophthalmic complications		Patients included	Patient included, date of the event is the minimum between "epistart" and "admidate"	Patient included if the first event was after the UK Biobank recruitment date (Field 53), date of the event is the minimum between "epistart" and "admidate"

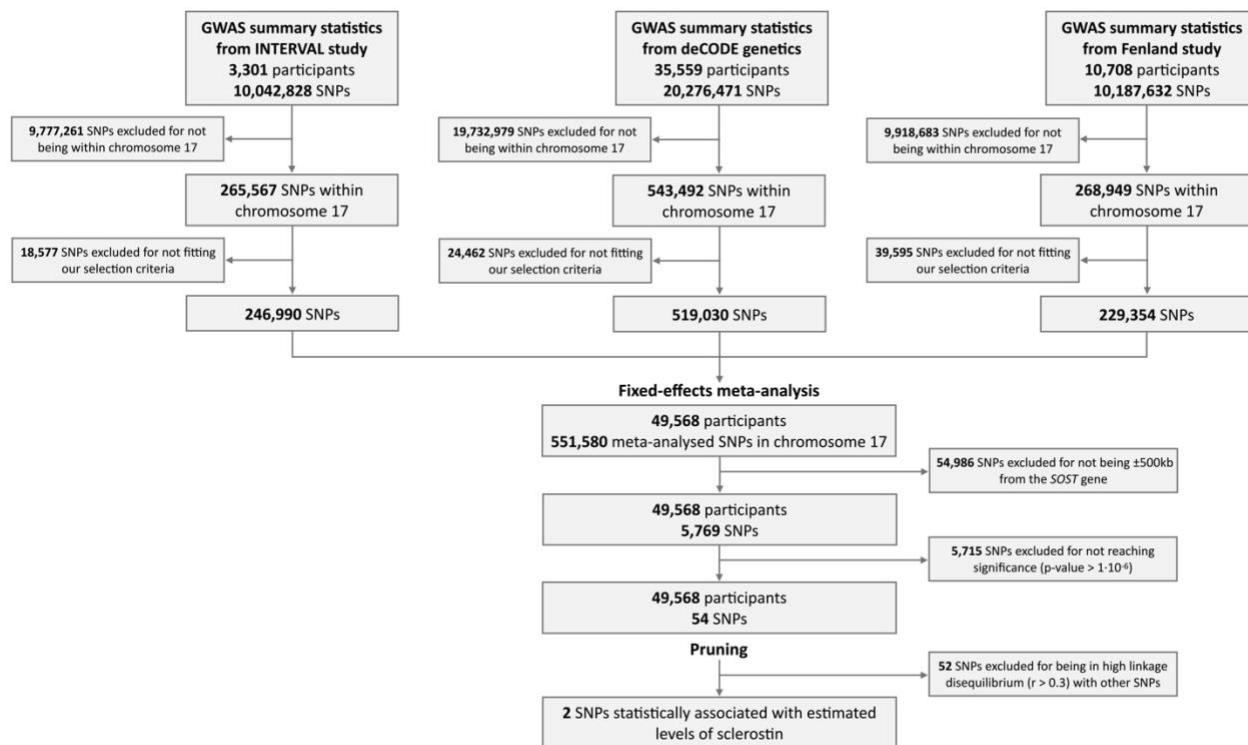
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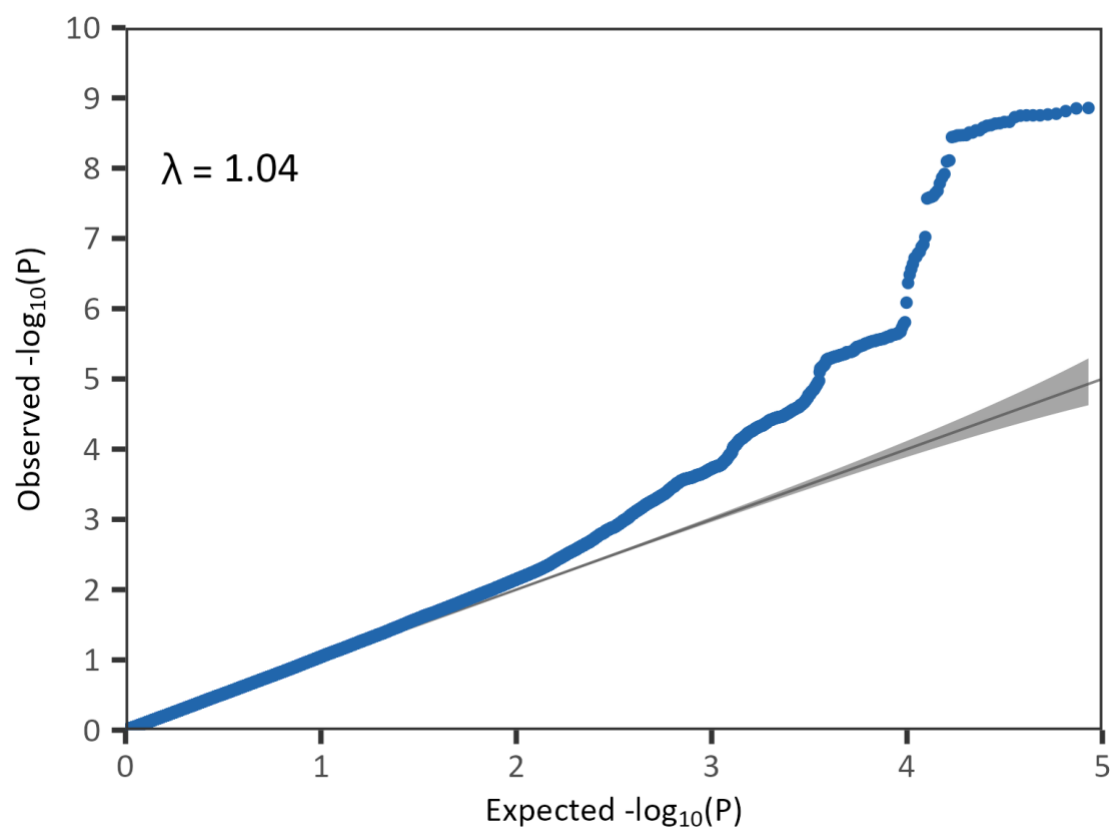
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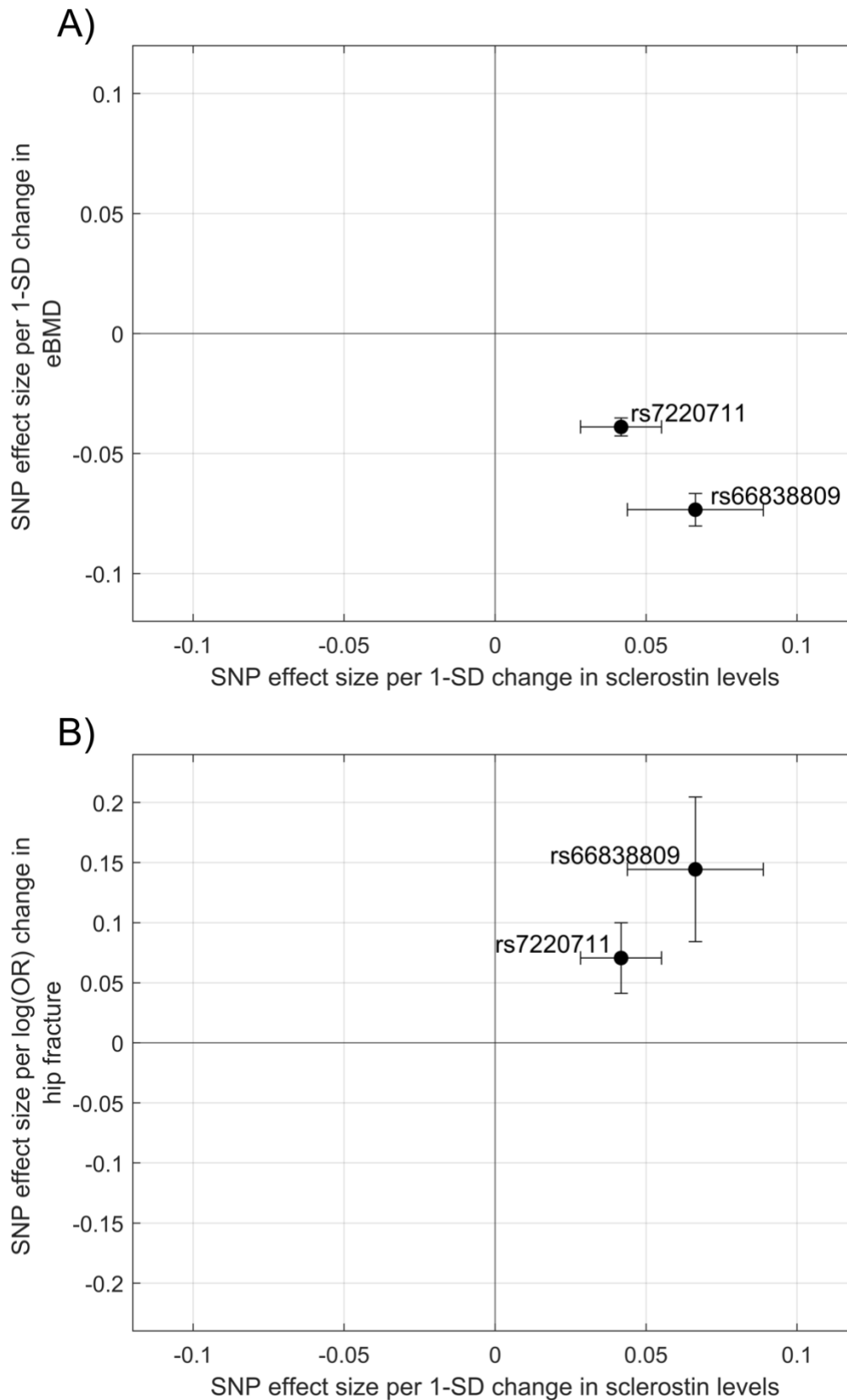


**Supplementary Fig. 1:** Flow chart of sclerostin meta-analysis and instrument selection.

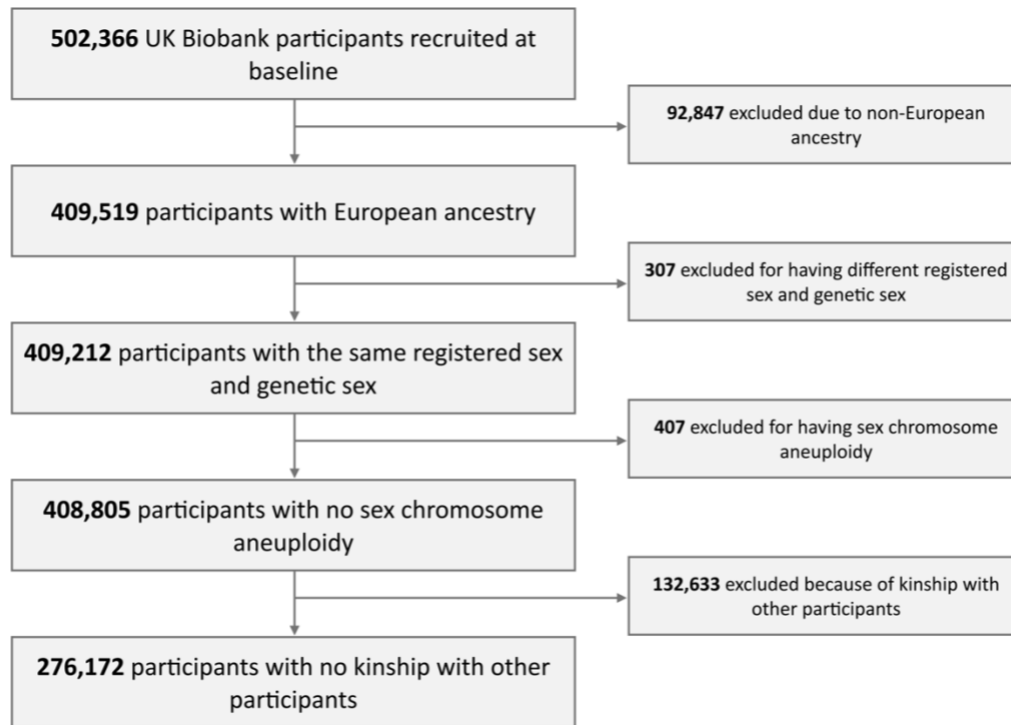




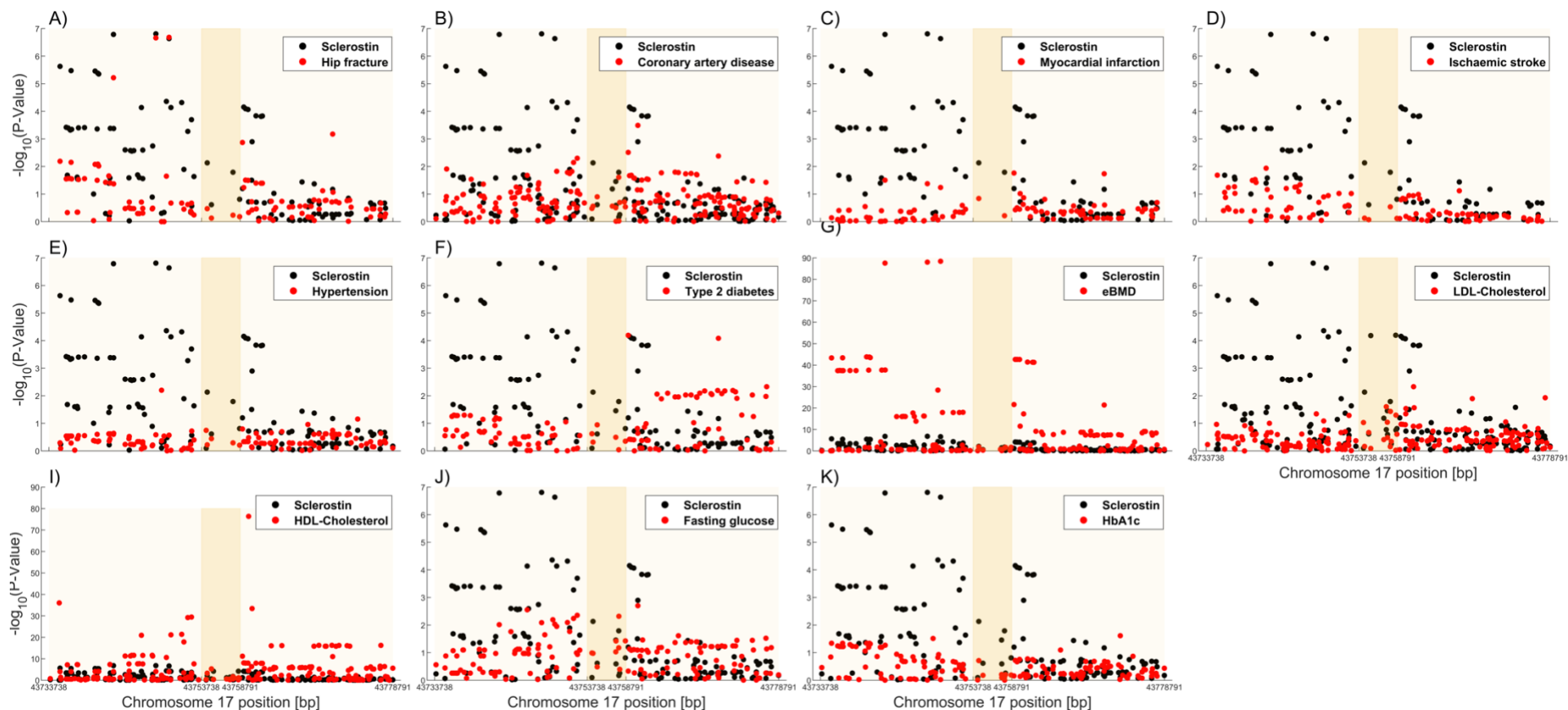
**Supplementary Fig. 2:** QQ plot of the fixed-effects meta-analysis results.



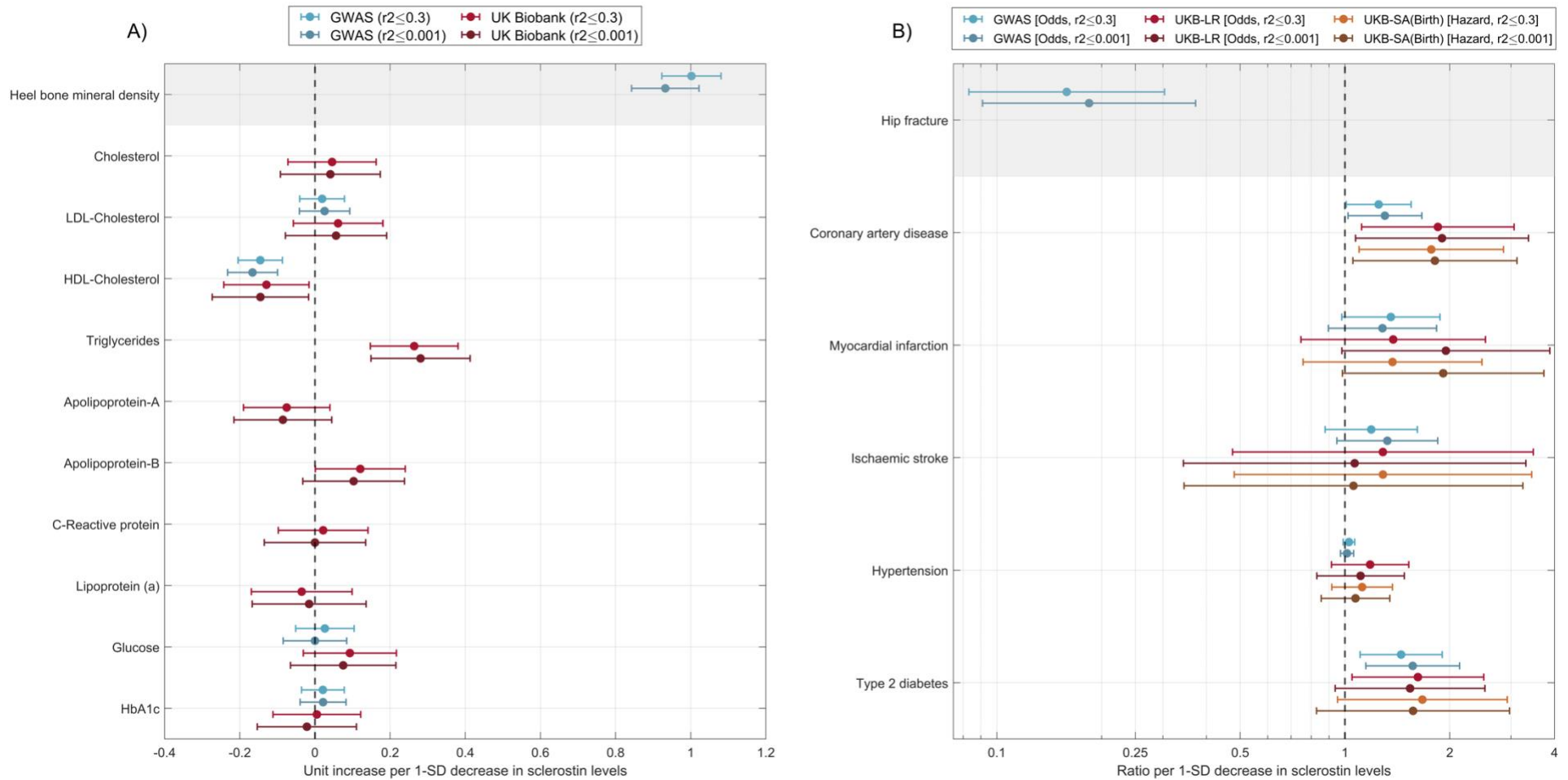
**Supplementary Fig. 3:** SNP effects on the positive control outcomes against SNP effects on the exposure. All SNPs with negative effects on the exposure are shown to be positive, with the sign of the effect on the outcome flipped. Error bars indicate the 95% confidence interval. **(A)** The vertical axis is the SNP effect size per 1-SD change in eBMD and, **(B)** the vertical axis is the SNP effect size for hip fracture.



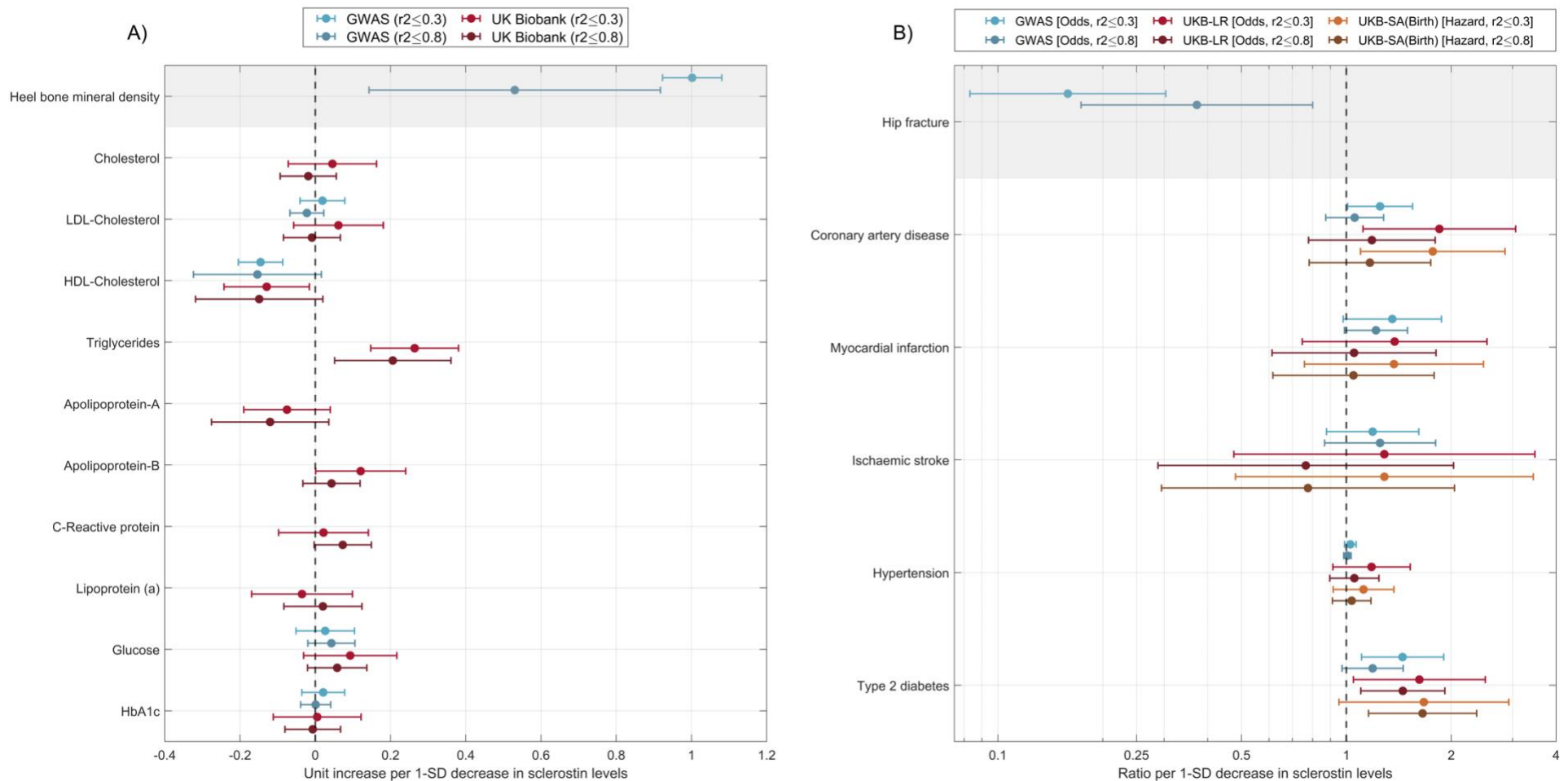
**Supplementary Fig 4:** Flow chart of the selection process of participants in the UK Biobank analysis.



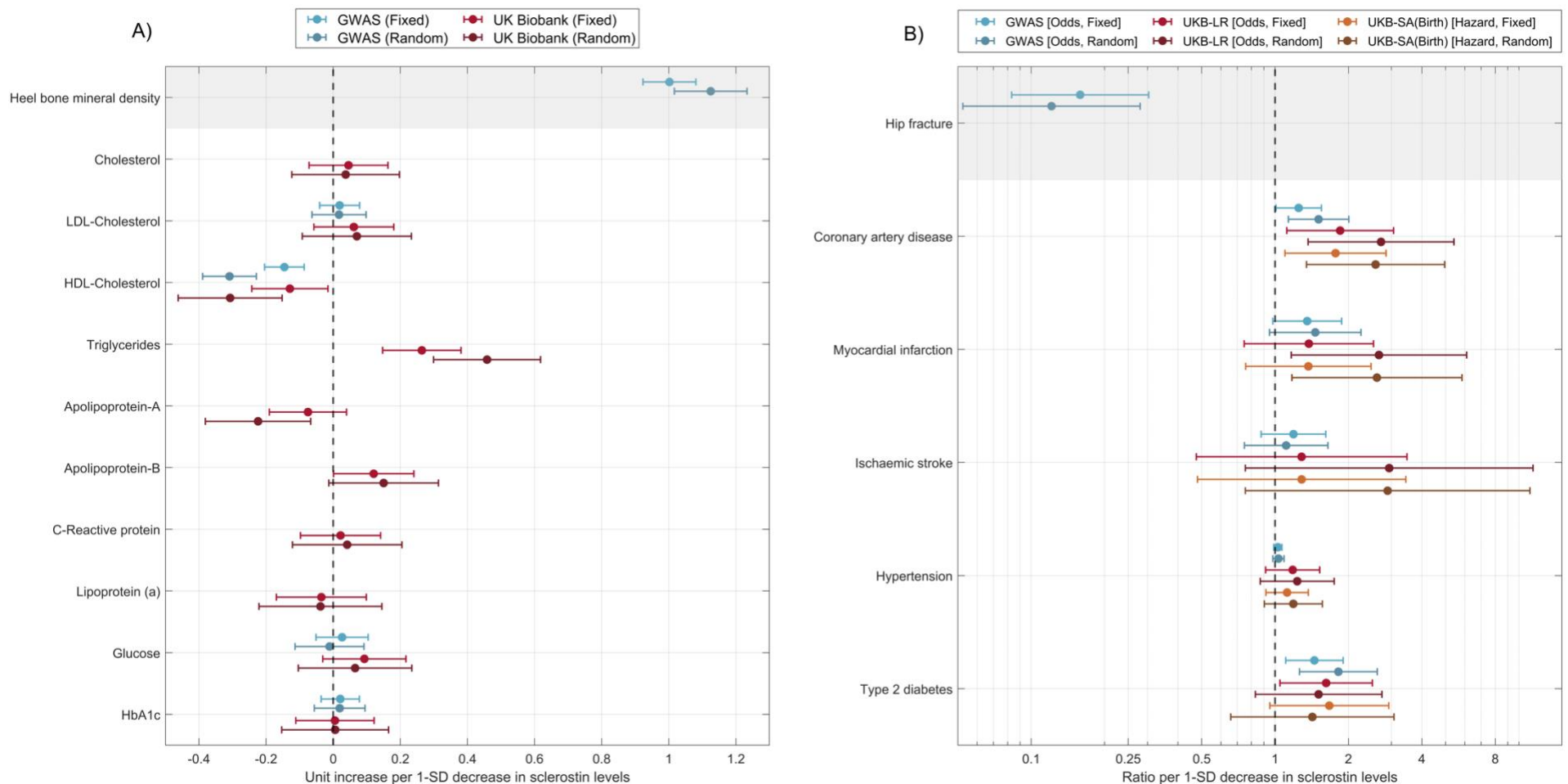
**Supplementary Fig. 5:** Colocalization analysis within  $\pm 20$ kb SOST gene. In dark yellow is the SOST gene. In light yellow is the area  $\pm 20$ kbp from the beginning and end of the SOST gene. **(A)** Regional plot for hip fracture, **(B)** Regional plot for coronary artery disease. **(C)** Regional plot for myocardial infarction. **(D)** Regional plot for ischaemic stroke. **(E)** Regional plot for hypertension. **(F)** Regional plot for type II diabetes mellitus. **(G)** Regional plot for estimated heel bone mineral density (eBMD). **(H)** Regional plot for LDL Cholesterol. **(I)** Regional plot for HDL Cholesterol. **(J)** Regional plot for fasting glucose. **(K)** Regional plot for HbA1c.



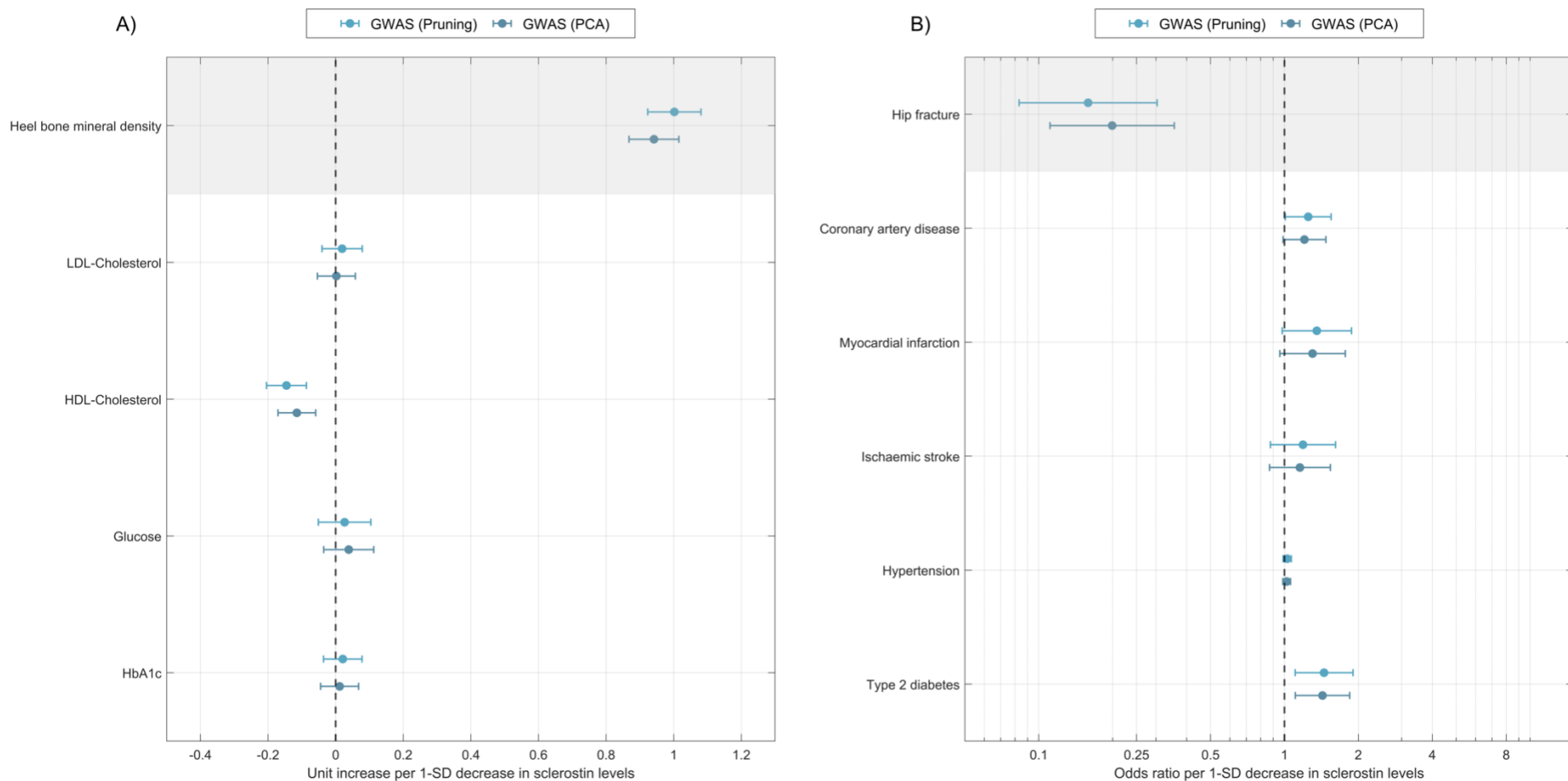
**Supplementary Fig. 6:** Stepwise pruning sensitivity analysis results using an  $r^2 \leq 0.001$ . Effect sizes were calculated using the Wald Ratio method. Results from the main analysis are represented using light colours, whereas those obtained using an  $r^2 \leq 0.001$  are shown using dark colours. Blue indicates the results using published GWAS summary statistics as the outcome; maroon the results obtained using a linear regression (for continuous outcomes) and logistic regression (for categorical outcomes) on the UK Biobank outcomes; and orange indicates the results using cox regression for UK Biobank survival outcomes. Error bars indicate the 95% confidence interval. **(A)** The horizontal axis shows the unit increase (95% CI) per 1 SD decrease in sclerostin levels. GWAS results for LDL and HDL-Cholesterol are in mg/dL, mmol/L for GWAS results of fasting glucose, % change for HbA1c and SD increase for the other outcomes. **(B)** The horizontal axis shows the odds/hazard ratio (95% CI) per 1 SD decrease in sclerostin levels. Note: UKB-LR = UK Biobank logistic regression, UKB-SA = UK Biobank survival analysis. Stepwise pruning sensitivity analysis results using an  $r^2 \leq 0.001$ .



**Supplementary Fig. 7:** Stepwise pruning sensitivity analysis results using an  $r^2 \leq 0.8$ . Effect sizes were calculated using the generalised inverse variance weighted method. Results from the main analysis are represented using light colours, whereas those obtained using an  $r^2 \leq 0.8$  are shown using dark colours. Blue indicates the results using published GWAS summary statistics as the outcome; maroon the results obtained using a linear regression (for continuous outcomes) and logistic regression (for categorical outcomes) on the UK Biobank outcomes; and orange indicates the results using cox regression for UK Biobank survival outcomes. Error bars indicate the 95% confidence interval. **(A)** The horizontal axis shows the unit increase (95% CI) per 1 SD decrease in sclerostin levels. GWAS results for LDL and HDL-Cholesterol are in mg/dL, mmol/L for GWAS results of fasting glucose, % change for HbA1c and SD increase for the other outcomes. **(B)** The horizontal axis shows the odds/hazard ratio (95% CI) per 1 SD decrease in sclerostin levels. Note: UKB-LR = UK Biobank logistic regression, UKB-SA = UK Biobank survival analysis.

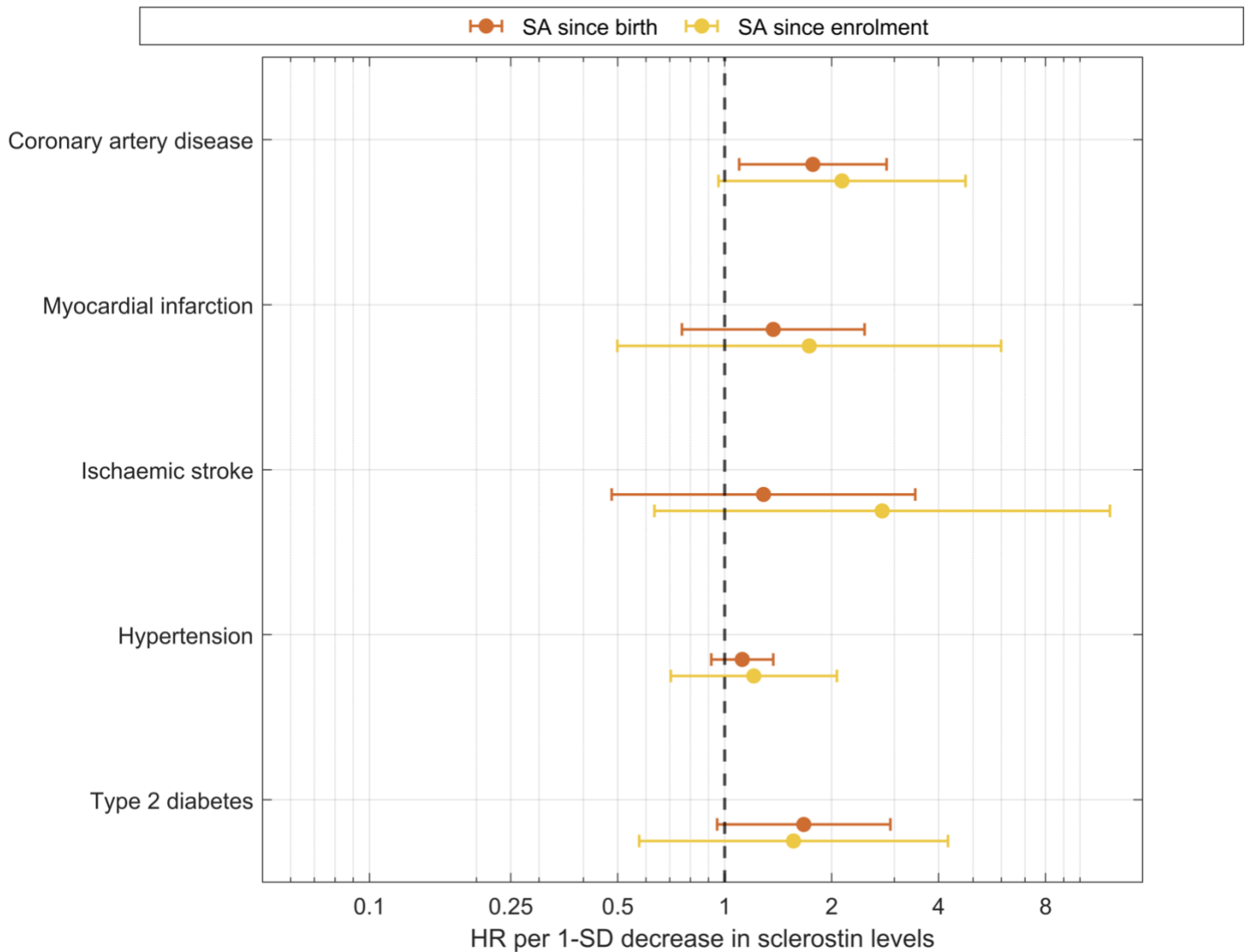


**Supplementary Fig. 8:** Random-effects sensitivity analysis results. Effect sizes were calculated using the generalised inverse variance weighted method. Results from the main analysis are represented using light colours, whereas random-effects results are shown using dark colours. Blue indicates the results using published GWAS summary statistics as the outcome; maroon the results obtained using a linear regression (for continuous outcomes) and logistic regression (for categorical outcomes) on the UK Biobank outcomes; and orange indicates the results using cox regression for UK Biobank survival outcomes. Error bars indicate the 95% confidence interval. **(A)** The horizontal axis shows the unit increase (95% CI) per 1 SD decrease in sclerostin levels. GWAS results for LDL and HDL-Cholesterol are in mg/dL, mmol/L for GWAS results of fasting glucose, % change for HbA1c and SD increase for the other outcomes. **(B)** The horizontal axis shows the odds/hazard ratio (95% CI) per 1 SD decrease in sclerostin levels. Note: UKB-LR = UK Biobank logistic regression, UKB-SA = UK Biobank survival analysis.



**Supplementary Fig. 9:** Principal components sensitivity analysis results. Results from the main analysis are shown using light colours, whereas principal components results are shown using dark colours. Error bars indicate the 95% confidence interval. **(A)** The horizontal axis shows the unit increase (95% CI) per 1 SD decrease in sclerostin levels. GWAS results for LDL and HDL-Cholesterol are in mg/dL, mmol/L for GWAS results of fasting glucose, % change for HbA1c and SD increase for the other outcomes. **(B)** The horizontal axis shows the odds/hazard ratio (95% CI) per 1 SD decrease in sclerostin levels. Note: UKB-LR = UK Biobank logistic regression, UKB-SA = UK Biobank survival analysis.





**Supplementary Fig. 10:** Survival analysis since UK Biobank enrolment sensitivity analysis results. Effect sizes were calculated using the generalised inverse variance weighted method. Main analysis results (survival outcomes since birth date) are shown in orange, whereas results from the sensitivity analysis (survival outcomes since UK Biobank enrolment) are shown in yellow. The horizontal axis shows the hazard ratio (HR) (95% CI) per 1 SD decrease in sclerostin levels. Error bars indicate the 95% confidence interval. Note: SA = Survival analysis.