

Supplementary Table 1. Details of studies and datasets used for analyses

ALSPAC indicates The Avon Longitudinal Study of Parents and Children; AGES, Age Gene/Environment Susceptibility Reykjavik Study; ARIC, The Atherosclerosis Risk in Communities Study (ARIC); BPROOF, B-Vitamins for the PRvention Of Osteoporotic Fractures; BLSA, The Baltimore Longitudinal Study of Aging; BMDCS, Bone Mineral Density in Childhood Study; CoLaus, Cohort Lausannoise; CHS, Cardiovascular Health Study; FHS, Framingham Heart Study; GOOD, Gothenburg Osteoporosis and Obesity Determinants; Generation R, The Generation R Study; HABC, Health ABC; LBC1936, Lothian Birth Cohort 1936; MrOS, Osteoporotic Fractures in Men USA; MrOS GBG, Osteoporotic Fractures in Men Gothenburg; MrOS MALMO, Osteoporotic Fractures in Men Malmo; NEO, Netherlands Epidemiology of Obesity; OGP, Ogliastra Genetic Park - Talana Study; ORGCADES,

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Study-II; RSIII, Rotterdam Study-III; RS, The Rotterdam Study; SHIP, Study of Health in Pomerania; TUK, TwinsUK; ULSAM, Uppsala Longitudinal

Study of Adult Men; Indiana, Indiana Sisters Cohort; NESDA, Netherlands Study of Depression and Anxiety; OGP–Talana, Ogliastro Genetic Park–Talana Study; GOOD, Gothenburg Osteoporosis and Obesity Determinants; Amish, Amish Family Osteoporosis Study; MDRD, Modification of Diet in Renal Disease.

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Supplementary Table 2. Characteristics of the single-nucleotide polymorphisms associated with serum 25-hydroxyvitamin D and calcium levels and their associations with type 2 diabetes, fasting glucose, fasting insulin, β -cell function and insulin resistance

Traits	SNP	Chr	Nearby gene	EA	EAF	Calcium or 25OHD level			Type 2 diabetes			Fasting Glucose		
						beta*	se	P	beta†	se	P	beta‡	se	P
Calcium	rs1801725	3	CASR	T	0.150	0.071	0.004	8.90×10 ⁻⁸⁶	0.026	0.011	0.015	-0.002	0.005	0.682
Calcium	rs1570669	20	CYP24A1	G	0.340	0.018	0.003	9.10×10 ⁻¹²	-0.011	0.008	0.150	-0.004	0.004	0.318
Calcium	rs1550532	2	DGKD	C	0.310	0.018	0.003	8.20×10 ⁻¹¹	-0.007	0.008	0.370	4.00×10 ⁻⁴	0.004	0.920
Calcium	rs7481584	11	CARS	G	0.700	0.018	0.003	1.20×10 ⁻¹⁰	-0.019	0.008	0.021	3.00×10 ⁻⁴	0.004	0.947
Calcium	rs780094	2	GCKR**	T	0.420	0.017	0.003	1.30×10 ⁻¹⁰	-0.068	0.008	9.20×10 ⁻¹⁹	-0.026	0.004	2.49×10 ⁻¹²
Calcium	rs7336933	13	DGKH/KIAA0564	G	0.850	0.022	0.004	9.10×10 ⁻¹⁰	0.010	0.010	0.320	0.003	0.005	0.516
Calcium	rs10491003	10	GATA3	T	0.090	0.027	0.005	4.80×10 ⁻⁹	-0.008	0.013	0.550	0.001	0.007	0.943
25OHD	rs3755967	4	GC	C	0.720	0.089	0.002	4.74×10 ⁻³⁴³	-0.006	0.008	0.450	0.001	0.004	0.845
25OHD	rs12785878	11	DHCR7	T	0.750	0.036	0.002	3.80×10 ⁻⁶²	-0.018	0.009	0.034	0.004	0.004	0.323
25OHD	rs10741657	11	CYP2R1	A	0.400	0.031	0.002	2.05×10 ⁻⁴⁶	-0.015	0.008	0.047	0.003	0.004	0.375
25OHD	rs17216707	20	CYP24A1	T	0.790	0.026	0.003	8.14×10 ⁻²³	-0.018	0.010	0.067	0.003	0.005	0.552
25OHD	rs10745742	12	AMDHD1	T	0.400	0.017	0.002	1.88×10 ⁻¹⁴	-0.016	0.008	0.039	-0.006	0.004	0.143
25OHD	rs8018720	14	SEC23A	G	0.180	0.017	0.003	4.72×10 ⁻⁹	0.001	0.010	0.940	-0.005	0.005	0.290
25OHD	rs117913124	11	CYP2R1	G	0.975	0.430††	0.020	1.50×10 ⁻⁸⁸	-0.021	0.024	0.390	NA	NA	NA
Traits	SNP	Chr	Nearby gene	EA	EAF	Fasting Insulin§	HOMA-B			HOMA-IR#				
Calcium	rs1801725	3	CASR	T	0.150	-0.001	0.006	0.898	0.002	0.005	0.674	-0.001	0.006	0.899
Calcium	rs1570669	20	CYP24A1	G	0.340	-0.007	0.004	0.070	-0.003	0.004	0.327	-0.006	0.004	0.129
Calcium	rs1550532	2	DGKD	C	0.310	0.011	0.004	0.009	0.006	0.004	0.109	0.009	0.004	0.043
Calcium	rs7481584	11	CARS	G	0.700	0.005	0.004	0.255	0.004	0.004	0.281	0.005	0.005	0.233
Calcium	rs780094	2	GCKR**	T	0.420	-0.015	0.004	9.77×10 ⁻⁵	-0.004	0.003	0.252	-0.020	0.004	7.63×10 ⁻⁷
Calcium	rs7336933	13	DGKH/KIAA0564	G	0.850	0.002	0.005	0.654	-0.003	0.005	0.556	0.003	0.006	0.613
Calcium	rs10491003	10	GATA3	T	0.090	-0.003	0.007	0.668	0.003	0.006	0.574	-0.002	0.007	0.747
25OHD	rs3755967	4	GC	C	0.720	-0.005	0.004	0.302	-0.006	0.004	0.122	-0.006	0.005	0.190
25OHD	rs12785878	11	DHCR7	T	0.750	0.007	0.004	0.091	0.004	0.004	0.224	0.006	0.004	0.168
25OHD	rs10741657	11	CYP2R1	A	0.400	0.006	0.004	0.139	0.003	0.003	0.391	0.007	0.004	0.079
25OHD	rs17216707	20	CYP24A1	T	0.790	0.007	0.005	0.175	0.005	0.005	0.257	0.009	0.006	0.089
25OHD	rs10745742	12	AMDHD1	T	0.400	0.001	0.004	0.894	0.004	0.003	0.299	0.000	0.004	0.950
25OHD	rs8018720	14	SEC23A	G	0.180	-0.004	0.005	0.398	-0.002	0.005	0.701	-0.006	0.005	0.262
25OHD	rs117913124	11	CYP2R1	G	0.975	NA	NA	NA	NA	NA	NA	NA	NA	NA

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Chr indicates chromosome; EA, effect allele; EAF, effect allele frequency; HOMA-B and HOMA-IR, homeostatic model assessment for β -cell function and insulin resistance; SE, standard error; SNP, single-nucleotide polymorphisms; 25OHD, 25-hydroxyvitamin D.

*The beta coefficients represent the change in serum levels of calcium (in mg/dL) and 25OHD (in ln-nmol/L for all SNPs but rs117913124, which is in SD units) for each additional effect allele.

†The beta coefficients represent the log odds ratio of type 2 diabetes for each additional effect allele.

‡The beta coefficients represent the change of level in mmol/l for each additional effect allele.

§The beta coefficients represent the change of natural log of level in pmol/l for each additional effect allele.

||The beta coefficients represent the change of natural log of score ($\text{HOMA-B} = 20 \times \text{insulin} / (\text{glucose} - 3.5)$) for each additional effect allele.

#The beta coefficients represent the change of natural log of score in $\text{pmol/l} \times \text{mmol/L}$ ($\text{HOMA-IR} = \text{glucose} \times \text{insulin} / 22.5$) for each additional effect allele.

**SNPs in GCKR gene were excluded from all analyses due to multiple pleiotropic associations with potential confounders.

††The beta coefficient represents the change in standard deviations of the standardized ln-transformed serum 25OHD levels.

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Supplementary Table 3. Characteristics of the single-nucleotide polymorphisms associated with serum parathyroid hormone levels and their associations with type 2 diabetes

Traits	SNP	Chr	Nearby gene	EA	S-PTH				Type 2 diabetes		
					EAF	beta*	se	P	beta†	se	P
S-PTH	rs6127099	20	CYP24A1	T	0.34	0.07	0.003	2.40×10^{-72}	0.017	0.009	0.044
S-PTH	rs4074995	5	RGS14	G	0.71	0.03	0.003	3.30×10^{-23}	-0.018	0.008	0.029
S-PTH	rs219779	21	CLDN14	G	0.75	0.04	0.003	8.90×10^{-22}	-0.010	0.009	0.230
S-PTH	rs4443100	22	RTDR1	G	0.32	0.02	0.003	4.10×10^{-11}	0.002	0.008	0.810
S-PTH	rs73186030	3	CASR	T	0.14	0.03	0.004	1.20×10^{-9}	0.030	0.011	0.006

Chr indicates chromosome; EA, effect allele; EAF, effect allele frequency; SE, standard error; SNP, single-nucleotide polymorphisms; S-PTH, serum parathyroid hormone.

*The beta coefficients represent the change in serum levels of parathyroid hormone (in pg/mL) for each additional effect allele.

†The beta coefficients represent the log odds ratio of type 2 diabetes for each additional effect allele.

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Supplementary Table 4. Related traits of the single-nucleotide polymorphisms associated with serum 25-hydroxyvitamin D from PhenoScanner V2

SNPs	EA	Nearby gene	Function	Related traits	Beta	P	Related traits	Beta	P	Related traits	Beta	P
rs3755967	C	<i>GC</i>	Transport	White blood cell count	0.026	3.61×10^{-11}	Myeloid white cell count	0.026	8.05×10^{-11}	Sum basophil neutrophil counts	0.025	1.85×10^{-10}
rs12785878	T	<i>DHCR7</i>	Synthesis	NA	NA	NA	NA	NA	NA	NA	NA	NA
rs10741657	A	<i>CYP2R1</i>	Synthesis	Height	0.010	2.30×10^{-8}	Hip circumference	0.011	3.22×10^{-6}	Leg fat-free mass right	0.007	5.84×10^{-6}
rs17216707	T	<i>CYP24A1</i>	Catabolism	Glomerular filtration rate creatinine	0.008	9.00×10^{-15}	log eGFR creatinine	-0.008	6.00×10^{-13}	Glomerular filtration rate	0.761	6.00×10^{-7}
rs10745742	T	<i>AMDHD1</i>	Catabolism	NA	NA	NA	NA	NA	NA	NA	NA	NA
rs8018720	G	<i>SEC23A</i>	Transport	NA	NA	NA	NA	NA	NA	NA	NA	NA
rs117913124	G	<i>CYP2R1</i>	Synthesis	NA	NA	NA	NA	NA	NA	NA	NA	NA
SNPs	EA	Nearby gene	Function	Related traits	Beta	P	Related traits	Beta	P	Related traits	Beta	P
rs3755967	C	<i>GC</i>	Transport	Granulocyte count	0.025	2.32×10^{-10}	Neutrophil count	0.025	3.22×10^{-10}	Sum neutrophil eosinophil counts	0.025	3.26×10^{-10}
rs12785878	T	<i>DHCR7</i>	Synthesis	NA	NA	NA	NA	NA	NA	NA	NA	NA
rs10741657	A	<i>CYP2R1</i>	Synthesis	Leg predicted mass right	0.007	7.57×10^{-6}	Leg predicted mass left	0.007	9.08×10^{-6}	NA	NA	NA
rs17216707	T	<i>CYP24A1</i>	Catabolism	Calculus of kidney and ureter	0.001	4.55×10^{-6}	Kidney stone or ureter stone/bladder stone	0.001	8.00×10^{-6}	Serum creatinine	NA	8.90×10^{-6}
rs10745742	T	<i>AMDHD1</i>	Catabolism	NA	NA	NA	NA	NA	NA	NA	NA	NA
rs8018720	G	<i>SEC23A</i>	Transport	NA	NA	NA	NA	NA	NA	NA	NA	NA
rs117913124	G	<i>CYP2R1</i>	Synthesis	NA	NA	NA	NA	NA	NA	NA	NA	NA

EA indicates effect allele; NA, not available; Web of PhenoScanner V2: <http://www.phenoscaner.medschl.cam.ac.uk/>

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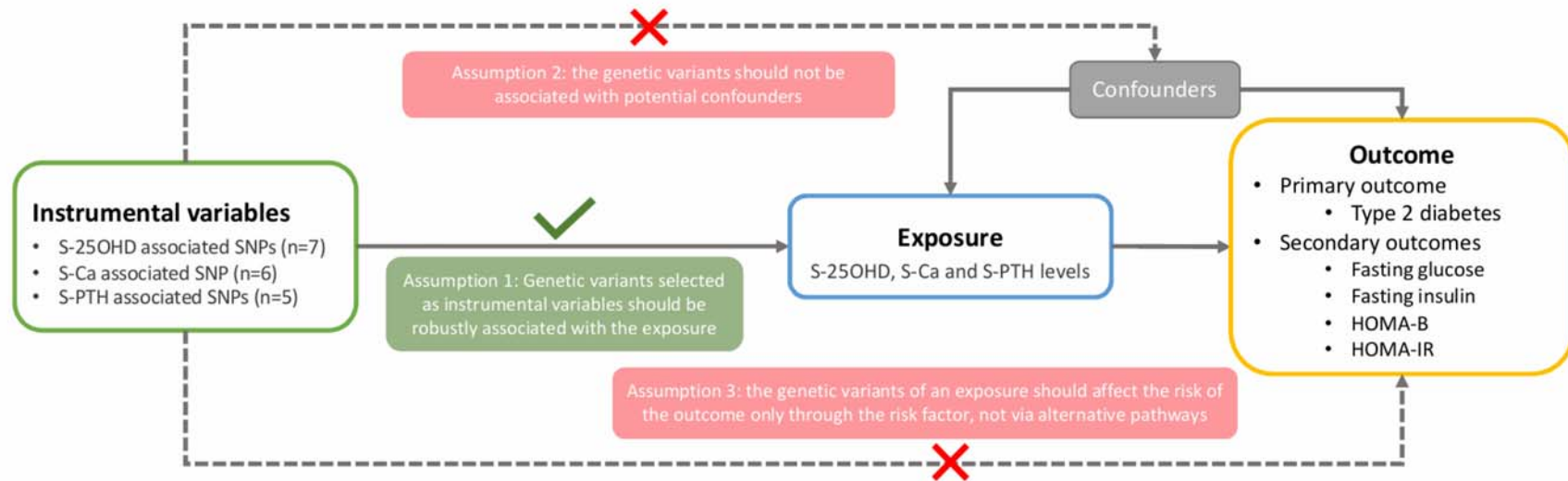
Supplementary Table 5. Related traits of the single-nucleotide polymorphisms associated with serum calcium from PhenoScanner V2

SNPs	EA	Nearby gene	Related traits	Beta	P	Related traits	Beta	P	Related traits	Beta	P
rs1801725	T	<i>CASR</i>	Pulse rate	-0.02	2.56×10^{-8}	Diastolic blood pressure	-0.02	1.50×10^{-6}	NA	NA	NA
rs1570669	G	<i>CYP24A1</i>	NA	NA	NA	NA	NA	NA	NA	NA	NA
rs1550532	C	<i>DGKD</i>	Bilirubin levels	NA	3.00×10^{-19}	Total serum bilirubin	NA	3.08×10^{-19}	NA	NA	NA
rs7481584	G	<i>CARS</i>	Sum basophil neutrophil counts	-0.01966	7.27×10^{-7}	Neutrophil count	-0.01948	8.76×10^{-7}	Granulocyte count	-0.02	1.28×10^{-6}
rs7336933	G	<i>DGKH/KIAA0564</i>	NA	NA	NA	NA	NA	NA	NA	NA	NA
rs10491003	T	<i>GATA3</i>	NA	NA	NA	NA	NA	NA	NA	NA	NA
SNPs	EA	Nearby gene	Related traits	Beta	P	Related traits	Beta	P	Related traits	Beta	P
rs1801725	T	<i>CASR</i>	NA	NA	NA	NA	NA	NA	NA	NA	NA
rs1570669	G	<i>CYP24A1</i>	NA	NA	NA	NA	NA	NA	NA	NA	NA
rs1550532	C	<i>DGKD</i>	NA	NA	NA	NA	NA	NA	NA	NA	NA
rs7481584	G	<i>CARS</i>	Sum neutrophil eosinophil counts	-0.02	1.68×10^{-6}	Myeloid white cell count	-0.02	2.21×10^{-6}	White blood cell count	-0.02	8.20×10^{-6}
rs7336933	G	<i>DGKH/KIAA0564</i>	NA	NA	NA	NA	NA	NA	NA	NA	NA
rs10491003	T	<i>GATA3</i>	NA	NA	NA	NA	NA	NA	NA	NA	NA

EA indicates effect allele; NA, not available; Web of PhenoScanner V2: <http://www.phenoscanter.medschl.cam.ac.uk/>

SUPPLEMENTARY DATA

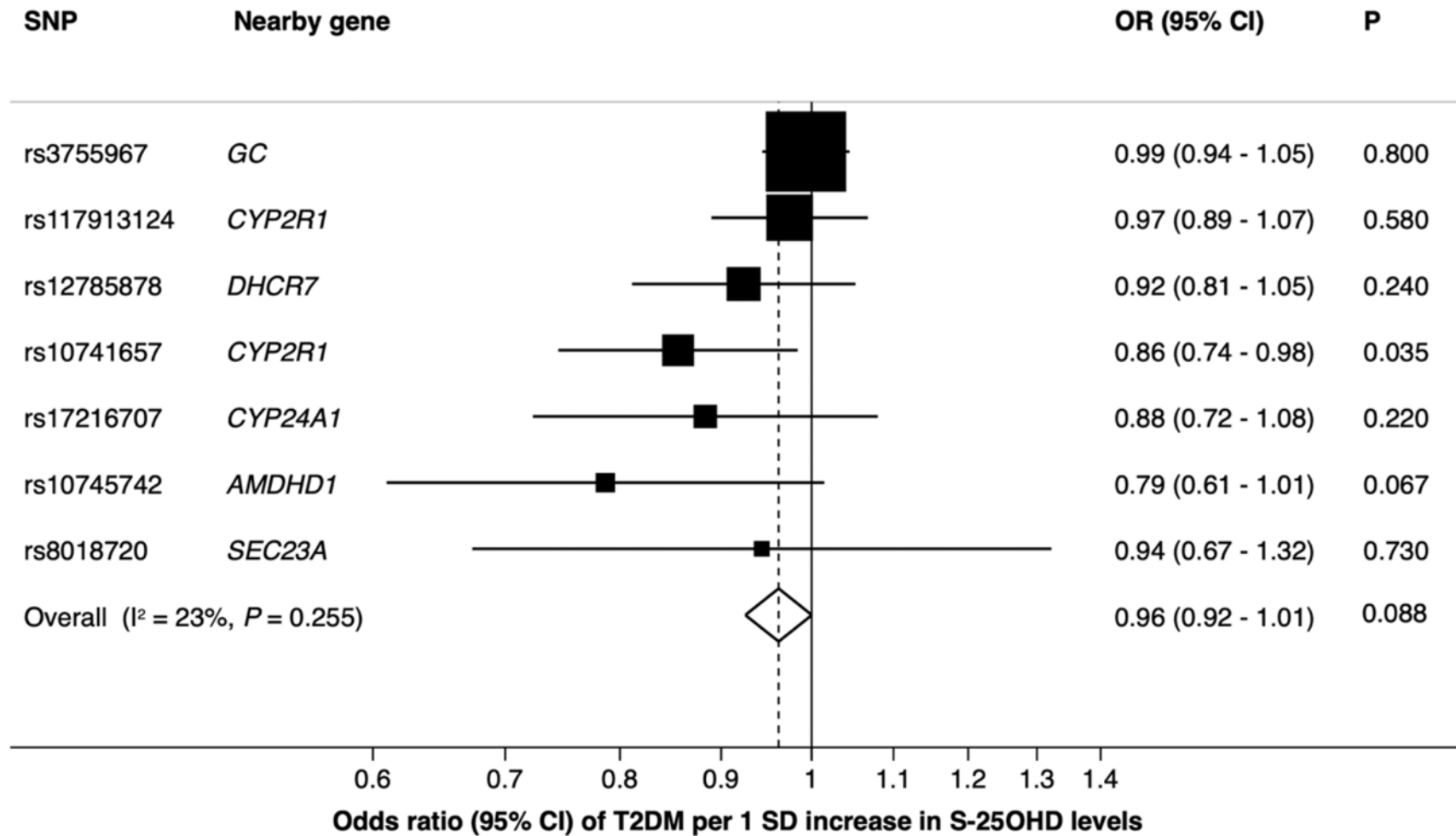
Supplementary Figure 1. Schematic diagram of the Mendelian randomization assumptions underpinning a Mendelian randomization analysis of the association between S-25OHD, S-Ca, S-PTH levels and type 2 diabetes and glycemic traits.



HOMA-B indicates homeostatic model assessment of beta-cell; HOMA-IR, homeostatic model assessment of insulin resistance; S-25OHD, serum 25-hydroxyvitamin D; S-Ca, serum calcium; S-PTH, serum parathyroid hormone.

SUPPLEMENTARY DATA

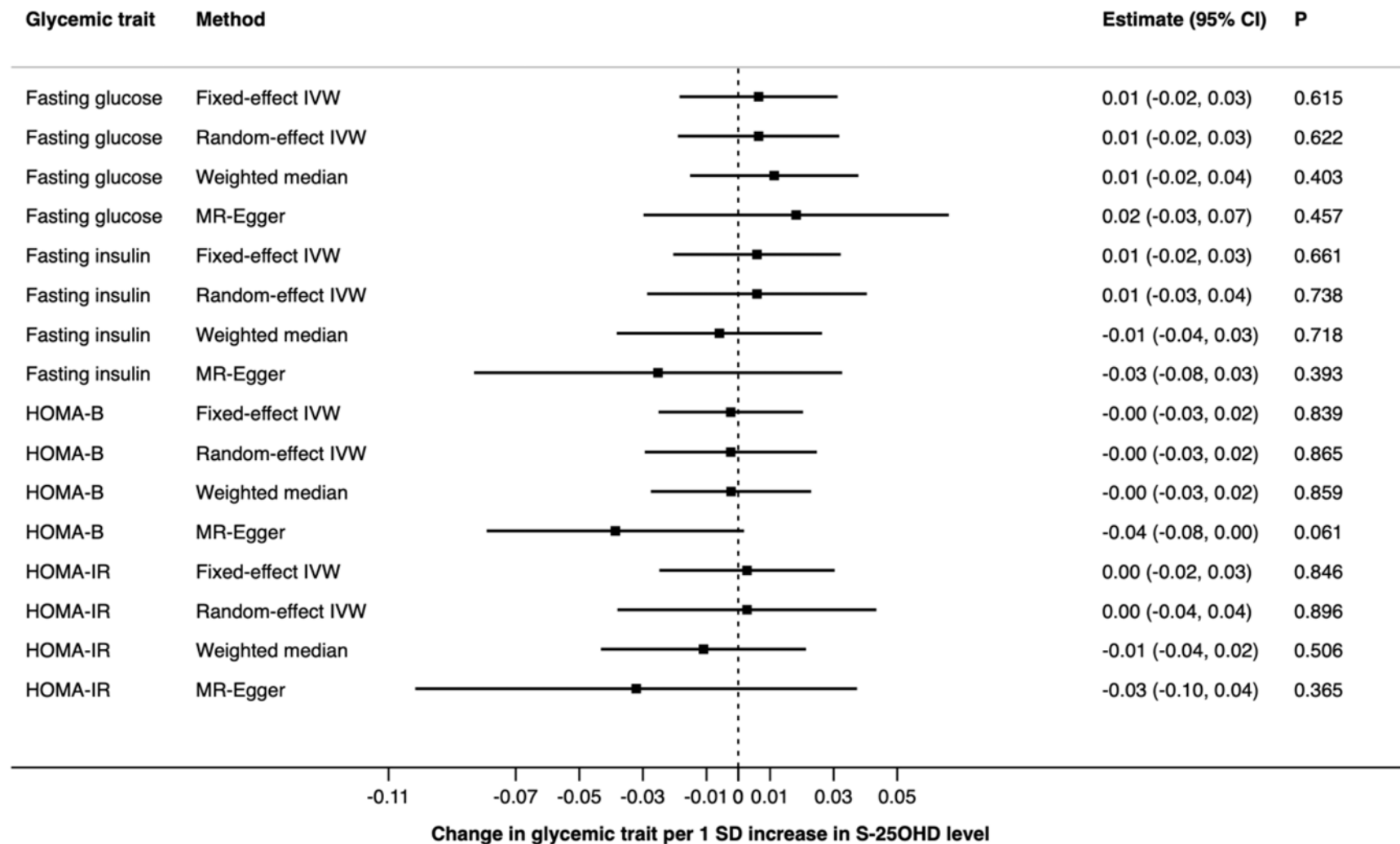
Supplementary Figure 2. Associations between serum 25OHD and the risk of type 2 diabetes based on body mass index unadjusted data in Mendelian Randomization analyses



CI indicates confidence interval; OR, odds ratio; SNP, single-nucleotide polymorphisms; S-25OHD, serum 25-hydroxyvitamin D.

SUPPLEMENTARY DATA

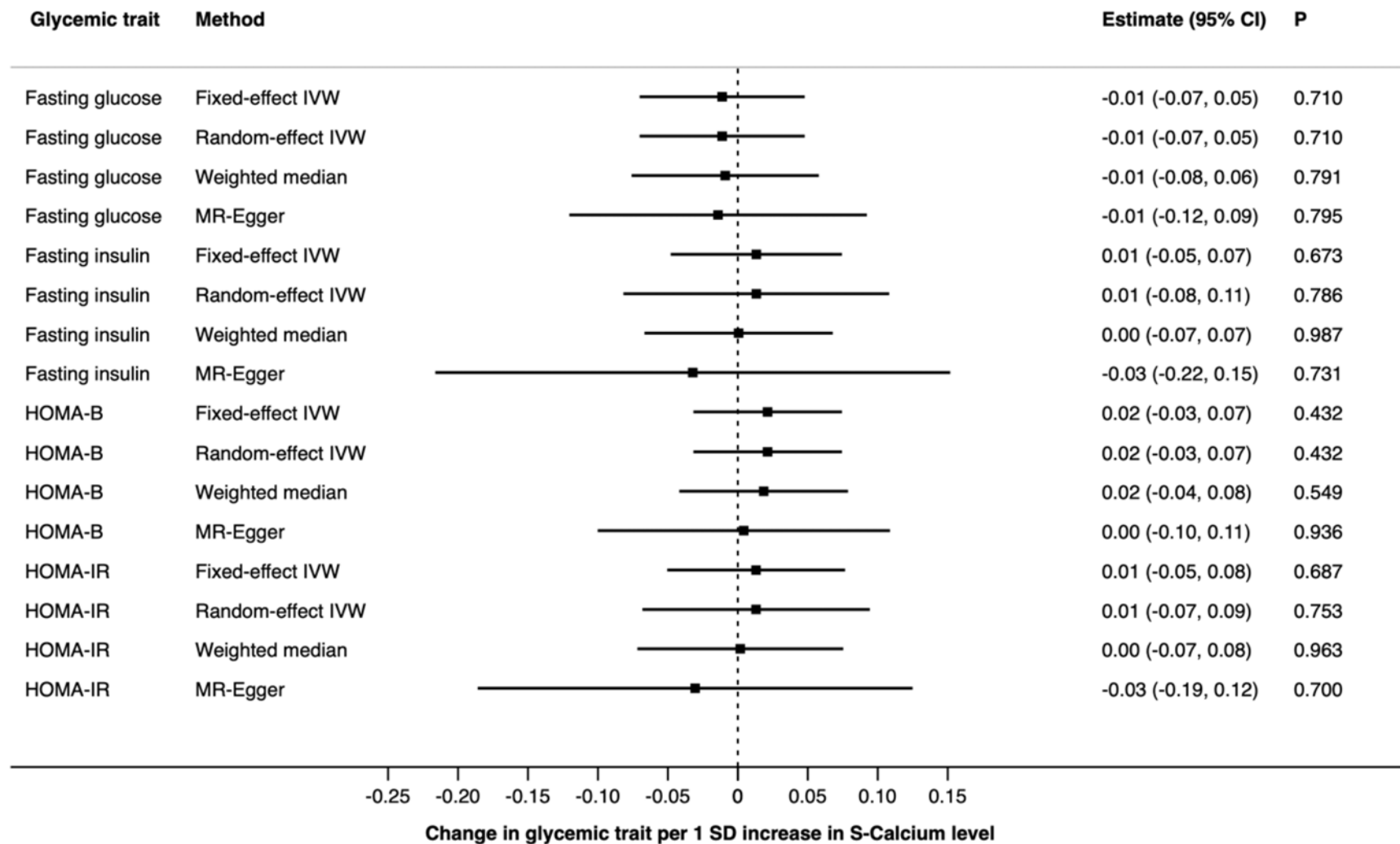
Supplementary Figure 3. Associations between serum 25OHD level and changes of glycemic traits from Mendelian Randomization Analyses



CI indicates confidence interval; HOMA-B, homeostatic model assessment for β -cell dysfunction; HOMA-IR, homeostatic model assessment for insulin resistance; IVW, inverse-variance weighted; MR-Egger, Mendelian randomization Egger regression; SD, standard deviation; S-25OHD, serum 25-hydroxyvitamin D;

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Supplementary Figure 4. Associations between serum calcium level and changes of glycemic traits in Mendelian Randomization Analyses



CI indicates confidence interval; HOMA-B, homeostatic model assessment for β -cell dysfunction; HOMA-IR, homeostatic model assessment for insulin resistance; IVW, inverse-variance weighted; MR-Egger, Mendelian randomization Egger regression; SD, standard deviation; S-Calcium, serum calcium;