Supplementary Material

Supplementary Methods

Overview of the study design

We conducted a multi-ancestry two-sample Mendelian Randomization analysis to assess the causal association of type 1 diabetes (T1D) and pancreatic cancer. We begin by acquiring GWAS data related to the T1D and selecting the suitable instrumental variable (IV) (single nucleotide polymorphism (SNP) and obtaining the effect of the IV on the exposure. Subsequently, we acquired the GWAS data of the outcome and obtained the effect of the above IV on pancreatic cancer (PCa). Then we conduct two sample MR analysis, accompanied by sensitivity analyses. All analyses mentioned above are conducted separately for European and East Asian populations.

Data sources

We extracted summary data from a meta-analysis of T1D GWAS, encompassing 47,319 participants of European ancestry [1]. The summary statistics utilized for PCa were derived from the most extensive GWAS meta-analysis to date, encompassing 411,013 participants from two major population-based cohorts: the UK Biobank and the Kaiser Permanente Genetic Epidemiology Research on Adult Health and Aging cohorts, both European ancestries [2].

For the East Asian population, we utilized T1D GWAS data from BioBank Japan (n = 133,251) [3]. The GWAS meta-analysis for PCa included 34,631 participants and was based on three Japanese studies: the Japan Pancreatic Cancer Research Consortium GWAS, the National Cancer Center GWAS, and the BioBank Japan GWAS [4].

To mitigate the influence of sample overlap on our findings, we meticulously selected the databases. Based on BBJ's public meta data and cohort enrollment records, the PCa cohort includes 422 participants overlapping with the T1D GWAS dataset—corresponding to 1.2% of the East Asian PCa cohort (422/34,631) and 0.3% of the East Asian T1D cohort (422/133,251). This degree of overlap is generally considered modest in two-sample MR settings.

Instrument variables selection and validation

We used genetic variants of T1D that passed the GWAS testing P value threshold ($< 5 \times 10^{-8}$) defined in the original study and had an effect allele frequency (EAF) > 0.01. We then clumped all those genetic variants to a linkage disequilibrium (LD) threshold of $r^2 < 0.001$ within ± 10,000 kilobases (kb) distance. When palindromic SNPs were present, the forward strand alleles were inferred using allele frequency information.

MR analysis

IV variants were matched to PCa datasets by orienting the effects of the exposure and the outcome to the same effect allele. If an instrument variant was missing in the outcome dataset, a genetic variant with high LD (r^2>0.8) to the variant was selected as a proxy instrument variant where possible. An inverse-variance weighted (IVW) approach was used to combine variant-level Wald ratio estimates into an overall effect estimate [5].

Validation of MR assumptions and sensitivity analyses

The study findings were reported following the guidelines outlined in STROBE-MR (Strengthening the Reporting of Mendelian Randomization Studies) [6]. We rigorously assessed the three crucial assumptions of Mendelian randomization through a comprehensive set of sensitivity analyses. To validate the relevance assumption, we determined the strength of genetic predictors using R^2 and F-statistics, with an F-statistic above 10 considered as evidence against weak instrument bias.

To scrutinize the exclusion restriction assumption, we conducted multiple sensitivity analyses, including MR-Egger regression, weighted median analysis, and both simple and weighted mode analyses. Furthermore, we utilized the Egger intercept and associated p-values to assess pleiotropy, while Cochran's Q test was employed to estimate the heterogeneity among instruments. We also depicted scatter plots to detect departures from MR assumptions and compare regression slopes from different MR analyses. Finally, a leave-one-out analysis was conducted to evaluate whether the causal relationship obtained in the study depended on or leaned towards a single SNP.

The statistical tests were two-sided. The statistical test for the MR analyses was considered statistically significant at $P < 0.05$. All the analyses were performed on the R platform (version 4.2.1). The “TwoSampleMR,” “Mendelian Randomization,” “ggplot2” packages were used for statistical analyses and data visualizations.

Statistical power calculation

Statistical power for the MR analyses was evaluated using the mRnd framework under the binary outcome model (https://shiny.cnsgenomics.com/mRnd/), which is appropriate for two-sample MR studies with dichotomous outcomes. Because the exposure of interest, T1D, is a binary trait, causal effects in MR are naturally estimated on the log-odds scale, whereas power calculations in mRnd assume a continuous exposure measured in standard deviation (SD) units. Therefore, power estimation was performed on the liability scale.

Under this framework, statistical power was assessed as a function of (i) the total outcome sample size, (ii) the proportion of cases in the outcome GWAS, (iii) the total proportion of variance in T1D explained by the genetic instruments (R^2), and (iv) the assumed causal effect size expressed per 1 SD increase in T1D liability. The transformation between the log-odds and liability scales depends on the assumed population prevalence of T1D, which was set to 6 per 10,000, consistent with epidemiological estimates in Asian populations. Power calculations were conducted assuming a two-sided type I error rate of $\alpha = 0.05$.

Because the exposure (T1D) is a binary trait, we first converted the MR causal estimate to the liability scale, which is required for valid power estimation in this setting. Specifically, assuming a population prevalence of T1D of 6 per 10,000, the observed MR estimate (OR = 1.25) corresponds to an odds ratio of approximately 2.19 per 1 standard deviation increase in T1D liability.

Using this liability-scaled effect size, we estimated statistical power based on the following parameters: total sample size of 167,881 participants, proportion of cases K = 0.0589, total variance in T1D explained by the genetic instruments ($R^2 \approx 0.0007$), and a two-sided significance level of $\alpha = 0.05$. Under these assumptions, the estimated statistical power was approximately 84%; however,

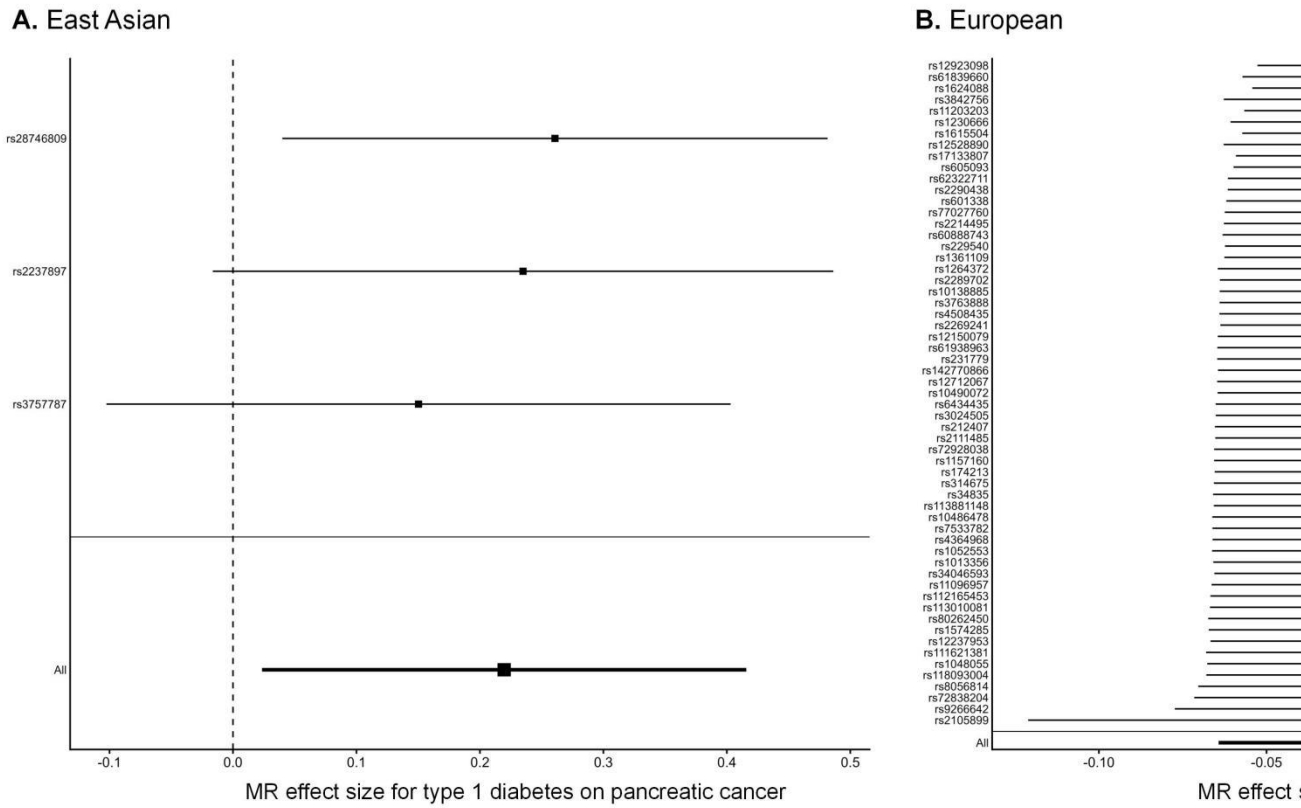
this estimate is conditional on the specified parameters and does not address residual bias risks or the limited sensitivity analyses in East Asians due to the small instrument count.

GWAS data quality control and population stratification correction

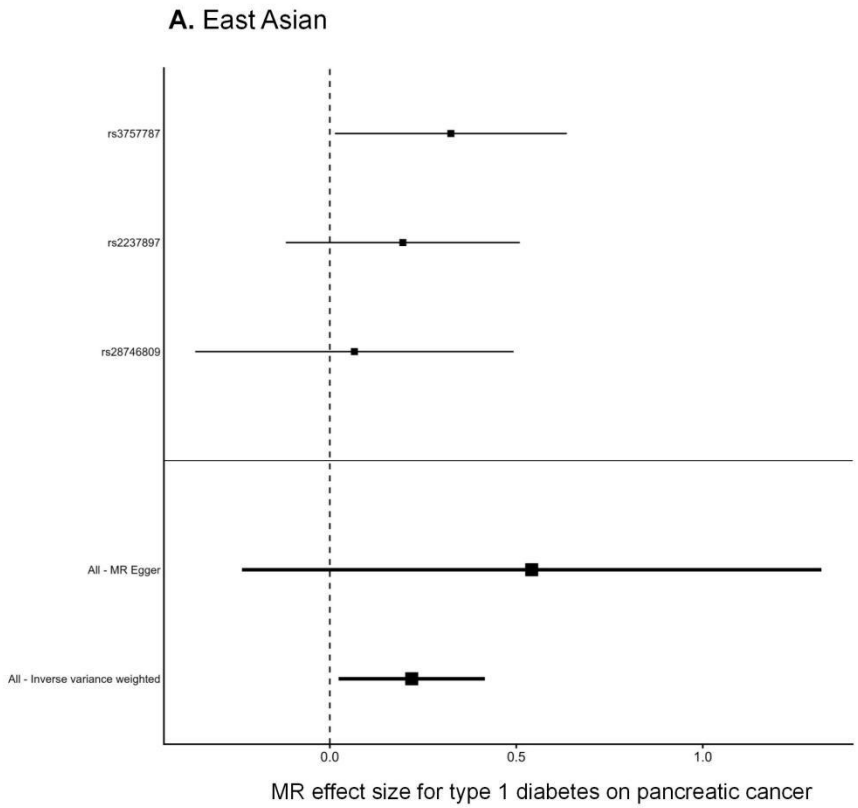
First, all T1D and PCa GWAS datasets used in our study underwent rigorous ancestry correction via PCA, following standard protocols for population stratification control [1]: For East Asian cohorts: T1D GWAS data (Biobank Japan) and PCa GWAS data (JaPAN, NCC, BBJ) were preprocessed by calculating the first 10 genetic principal components (PCs) using 1000 Genomes Project East Asian (EAS) reference panel (CHB, JPT, CHS, CDX, KHV). These 10 PCs were included as covariates in the GWAS regression models to adjust for subpopulation differences (e.g., between Japanese and Chinese subgroups). For European cohorts: T1D and PCa GWAS data were corrected using the first 10 PCs derived from the 1000 Genomes Project European (EUR) reference panel (CEU, TSI, FIN, GBR, IBS), accounting for continental substructure (e.g., Northern vs. Southern European ancestry). The GWAS summary statistics we used were generated after these PCA adjustments, ensuring that population stratification was already controlled at the source of the data.

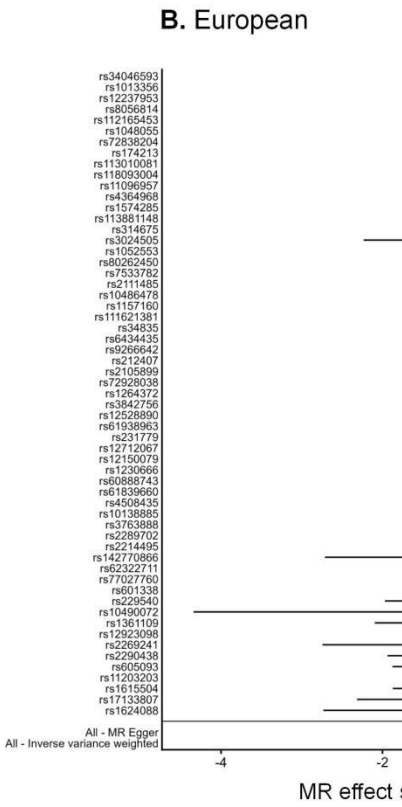
Second, involving ancillary control: Ancestry-Specific IV Selection and LD Reference Panels. (1) Strict ancestry matching for IVs: IVs were selected exclusively from ancestry-matched GWAS datasets—no cross-ancestry SNPs were used. For example, East Asian IVs were filtered from East Asian T1D GWAS data only, with allele frequency (AF) matching to the EAS reference panel (AF difference < 0.05). This avoids bias from allele frequency divergence between populations. (2) Ancestry-specific LD pruning: LD pruning ($r^2 < 0.001$) to select independent IVs was performed using population-matched LD reference panels (EAS for East Asians, EUR for Europeans). This prevents overrepresentation of SNPs with population-specific LD patterns that could mimic stratification-related effects.

Supplementary Figure S1. Leave one out analysis for type 1 diabetes on pancreatic cancer



Supplementary Figure S2. Single-SNP Wald ratio estimates for East Asians and Europeans





Supplemental Table SI. Data sources

Ancestry	Traits	Consortium	Sample size	N case	N control	Journal	Year	PMID	Citation
European	Type 1 diabetes	Meta analysis	47319	20017	27302	Nat Genet	2021	34127860	[15]
	Pancreatic cancer	UKB, GERA	411013	663	410350	Nat Commun	2020	32887889	[16]
East Asian	Type 1 diabetes	BBJ	133251	1219	132032	Nat Genet	2021	34594039	[17]
	Pancreatic cancer	JaPAN, NCC, BBJ	34631	2039	32592	Nat Commun	2020	32581250	[18]

N case, number of case; N control, number of control; UKB, UK Biobank; GERA, Kaiser Permanente Genetic Epidemiology Research on Adult Health and Aging cohorts; JaPan, the Japan Pancreatic Cancer Research Consortium; NCC, the National Cancer Center; BBJ, Biobank Japan.

Supplementary Table SII. The characteristic of instrumental variable of type 1 diabetes in European population

No	SNP	Chr	Position	Effect allele	Other allele	beta	se	P value	Sample size	R2	F-Statistics
1	rs1013356	4	165686352	C	T	0.209	0.035	3.88 E-09	47319	0.0007	34.7
2	rs10138885	14	98019483	G	A	-0.117	0.017	1.41 E-11	47319	0.001	45.7
3	rs1048055	20	1629416	C	A	0.128	0.017	1.33 E-13	47319	0.0012	54.8
4	rs10486478	7	26779846	T	C	-0.136	0.019	6.35 E-13	47319	0.0011	51.7
5	rs10490072	2	60442796	C	T	-0.108	0.018	3.47 E-09	47319	0.0007	34.9
6	rs1052553	17	45996523	G	A	-0.144	0.019	5.02 E-14	47319	0.0012	56.7
7	rs11096957	4	38774870	G	T	0.098	0.017	6.23 E-09	47319	0.0007	33.8
8	rs111621381	6	28786682	G	A	-0.385	0.033	1.07 E-30	47319	0.0028	132.7
9	rs11203203	21	42416077	A	G	0.138	0.016	2.03 E-17	47319	0.0015	72.1
10	rs112165453	2	203800092	T	C	0.339	0.05	1.34 E-11	47319	0.001	45.8
11	rs113010081	3	46415921	C	T	-0.17	0.026	1.31 E-10	47319	0.0009	41.3
12	rs113881148	4	973543	A	C	0.096	0.017	1.78 E-08	47319	0.0007	31.7
13	rs1157160	5	40504318	C	T	-0.101	0.017	1.95 E-09	47319	0.0008	36
1	rs11809	10	6132450	T	C	-0.7	0.1	1.92	473	0.00	49.6

4	3004					64	08	E-12	19	1	
15	rs12150079	17	39869164	A	G	0.116	0.017	3.89 E-12	47319	0.001	48.2
16	rs12237953	9	99606259	C	T	-0.111	0.019	7.88 E-09	47319	0.0007	33.3
17	rs1230666	1	113630788	G	A	-0.461	0.021	2.90 E-110	47319	0.0104	497.8
18	rs12528890	6	33121826	T	C	-0.648	0.029	1.20 E-111	47319	0.0105	504.1
19	rs1264372	6	30801949	T	C	0.638	0.017	1.00 E-200	47319	0.0283	1375.9
20	rs12712067	2	100147438	T	G	-0.093	0.017	2.31 E-08	47319	0.0007	31.2
21	rs12923098	16	11083196	C	T	-0.2	0.017	7.77 E-31	47319	0.0028	133.3
22	rs1361109	6	126449997	T	C	0.145	0.016	7.71 E-20	47319	0.0018	83.1
23	rs142770866	19	10414696	A	G	-0.176	0.03	4.50 E-09	47319	0.0007	34.4
24	rs1574285	9	4283137	T	G	-0.13	0.016	3.94 E-16	47319	0.0014	66.3
25	rs1615504	18	69859408	C	T	-0.117	0.016	1.24 E-13	47319	0.0012	54.9
26	rs1624088	8	11877717	A	G	-0.106	0.019	1.63 E-08	47319	0.0007	31.9
27	rs17133807	7	50409989	A	G	-0.1	0.018	2.96 E-08	47319	0.0006	30.7
28	rs174213	14	68843795	T	C	-0.112	0.017	7.14 E-11	47319	0.0009	42.5
29	rs2105899	6	32622696	C	T	1.512	0.033	1.00 E-20	47319	0.0417	2060.8

								0			
30	rs2111485	2	162254026	G	A	0.144	0.016	1.52E-18	47319	0.0016	77.2
31	rs212407	6	159049385	A	G	0.109	0.017	5.53E-11	47319	0.0009	43
32	rs2214495	7	50987857	C	A	0.313	0.046	1.64E-11	47319	0.001	45.4
33	rs2269241	1	63643100	C	T	0.115	0.019	3.26E-09	47319	0.0007	35
34	rs2289702	15	78944951	T	C	-0.264	0.028	3.06E-21	47319	0.0019	89.5
35	rs2290438	17	4019835	T	G	-0.114	0.021	2.79E-08	47319	0.0007	30.8
36	rs229540	22	37195250	G	T	0.101	0.016	2.69E-10	47319	0.0008	39.9
37	rs231779	2	203869764	T	C	0.204	0.016	2.30E-36	47319	0.0033	158.6
38	rs3024505	1	206766559	A	G	-0.163	0.022	3.05E-13	47319	0.0011	53.2
39	rs314675	19	46692822	C	T	-0.156	0.024	5.64E-11	47319	0.0009	42.9
40	rs34046593	4	26109971	A	G	0.104	0.017	6.79E-10	47319	0.0008	38.1
41	rs34835	16	28487970	G	A	-0.122	0.016	6.25E-14	47319	0.0012	56.3
42	rs3763888	11	35285601	C	T	0.093	0.016	7.17E-09	47319	0.0007	33.5
43	rs3842756	11	2159542	T	C	-0.738	0.023	1.00E-200	47319	0.0213	1029.8
44	rs4364968	10	6461769	A	C	-0.089	0.016	4.59E-08	47319	0.0006	29.9
45	rs4508435	16	11384846	G	T	-0.106	0.018	7.95E-09	47319	0.0007	33.3

46	rs601338	19	48703417	A	G	0.111	0.016	1.48E-12	47319	0.0011	50.1
47	rs605093	11	128734337	T	G	0.104	0.016	5.16E-11	47319	0.0009	43.1
48	rs60888743	10	88291560	G	A	-0.179	0.019	6.18E-22	47319	0.002	92.7
49	rs61839660	10	6052734	T	C	-0.463	0.03	1.13E-52	47319	0.0049	233.3
50	rs61938963	12	56053020	T	C	0.23	0.016	3.26E-44	47319	0.0041	194.5
51	rs62322711	4	122497180	G	A	0.156	0.02	3.85E-15	47319	0.0013	61.8
52	rs6434435	2	191089138	A	G	-0.117	0.021	3.20E-08	47319	0.0006	30.6
53	rs72838204	6	29821306	T	C	0.362	0.031	8.55E-32	47319	0.0029	137.7
54	rs72928038	6	90267049	A	G	0.172	0.02	1.46E-17	47319	0.0015	72.8
55	rs7533782	1	200863456	G	A	0.133	0.02	2.41E-11	47319	0.0009	44.6
56	rs77027760	6	137680924	A	G	-0.131	0.021	4.53E-10	47319	0.0008	38.9
57	rs80262450	18	12818923	A	G	0.225	0.023	7.44E-23	47319	0.002	96.9
58	rs8056814	16	75218429	A	G	0.266	0.027	3.50E-23	47319	0.0021	98.4
59	rs9266642	6	31379424	T	C	0.703	0.023	1.00E-200	47319	0.0195	941.7

Supplementary Table SIII. The characteristic of instrumental variable of type 1 diabetes in East Asian population

No	SNP	Chr	Position	Nearest gene	Effect allele	Other allele	Effect allele frequency	Beta	SE	F
1	rs2237897	11	2858546	KCNQ1	T	C	0.391	-0.243	0.043	1
2	rs28746809	6	32633159	HLA-DQB1	C	T	0.384	0.247	0.045	3
3	rs3757787	7	127258384	PAX4	T	C	0.088	0.436	0.077	1

Supplementary Table SIV. Steiger directionality test for instrumental variables

Ancestry	Instrumental SNP	Effect allele	Other allele	R2_exposure	R2_outcome	Direction	Steiger test P
East Asian	rs2237897	T	C	2.40E-04	4.32E-05	Exposure → Outcome	1.39E-01
	rs28746809	C	T	2.29E-04	2.76E-06	Exposure → Outcome	2.80E-02
	rs3757787	T	C	2.40E-04	1.26E-04	Exposure → Outcome	4.73E-01
European	rs1013356	C	T	7.32E-04	2.98E-06	Exposure → Outcome	1.78E-07
	rs10138885	G	A	9.64E-04	4.48E-07	Exposure → Outcome	3.85E-10
	rs1048055	C	A	1.16E-03	4.22E-06	Exposure → Outcome	4.51E-11
	rs10486478	T	C	1.09E-03	4.68E-07	Exposure → Outcome	2.57E-11
	rs10490072	C	T	7.37E-04	3.45E-07	Exposure → Outcome	4.44E-08
	rs1052553	G	A	1.20E-03	7.45E-07	Exposure → Outcome	3.58E-12
	rs11096957	G	T	7.13E-04	1.65E-06	Exposure → Outcome	1.63E-07
	rs111621381	G	A	2.80E-03	9.26E-07	Exposure → Outcome	9.72E-27
	rs11203203	A	G	1.52E-03	9.74E-06	Exposure → Outcome	1.39E-13
	rs112165453	T	C	9.66E-04	2.81E-06	Exposure → Outcome	1.37E-09
	rs113010081	C	T	8.72E-04	2.40E-06	Exposure → Outcome	8.17E-09
	rs113881148	A	C	6.70E-04	6.52E-0	Exposure →	2.90E-07

					7	Outcome	
	rs1157160	C	T	7.61E-04	2.15E-07	Exposure → Outcome	2.31E-08
	rs118093004	T	C	1.05E-03	3.72E-06	Exposure → Outcome	3.65E-10
	rs12150079	A	G	1.02E-03	9.59E-08	Exposure → Outcome	7.61E-11
	rs12237953	C	T	7.03E-04	3.72E-06	Exposure → Outcome	4.04E-07
	rs1230666	G	A	1.04E-02	1.08E-06	Exposure → Outcome	8.76E-97
	rs12528890	T	C	1.05E-02	3.87E-07	Exposure → Outcome	8.56E-99
	rs1264372	T	C	2.83E-02	8.58E-08	Exposure → Outcome	8.01E-267
	rs12712067	T	G	6.59E-04	4.60E-08	Exposure → Outcome	1.55E-07
	rs12923098	C	T	2.81E-03	1.29E-05	Exposure → Outcome	2.22E-24
	rs1361109	T	C	1.75E-03	2.48E-06	Exposure → Outcome	9.84E-17
	rs142770866	A	G	7.26E-04	3.12E-07	Exposure → Outcome	5.39E-08
	rs1574285	T	G	1.40E-03	1.77E-06	Exposure → Outcome	1.06E-13
	rs1615504	C	T	1.16E-03	9.80E-06	Exposure → Outcome	1.85E-10
	rs1624088	A	G	6.74E-04	2.11E-05	Exposure → Outcome	1.07E-05
	rs17133807	A	G	6.49E-04	8.28E-06	Exposure → Outcome	3.21E-06
	rs174213	T	C	8.97E-04	7.16E-07	Exposure → Outcome	2.01E-09

	rs2105899	C	T	4.17E-02	4.48E-06	Exposure → Outcome	0
	rs2111485	G	A	1.63E-03	1.45E-07	Exposure → Outcome	1.70E-16
	rs212407	A	G	9.08E-04	5.32E-08	Exposure → Outcome	7.28E-10
	rs2214495	C	A	9.58E-04	1.42E-06	Exposure → Outcome	8.70E-10
	rs2269241	C	T	7.40E-04	1.24E-06	Exposure → Outcome	7.71E-08
	rs2289702	T	C	1.89E-03	5.29E-07	Exposure → Outcome	1.29E-18
	rs2290438	T	G	6.52E-04	3.65E-06	Exposure → Outcome	1.14E-06
	rs229540	G	T	8.42E-04	2.93E-06	Exposure → Outcome	2.32E-08
	rs231779	T	C	3.34E-03	4.58E-08	Exposure → Outcome	1.60E-32
	rs3024505	A	G	1.12E-03	1.22E-07	Exposure → Outcome	8.37E-12
	rs314675	C	T	9.07E-04	4.99E-07	Exposure → Outcome	1.37E-09
	rs34046593	A	G	8.04E-04	4.62E-06	Exposure → Outcome	6.66E-08
	rs34835	G	A	1.19E-03	2.55E-07	Exposure → Outcome	2.57E-12
	rs3763888	C	T	7.07E-04	4.67E-07	Exposure → Outcome	9.37E-08
	rs3842756	T	C	2.13E-02	4.54E-07	Exposure → Outcome	9.41E-197
	rs4364968	A	C	6.31E-04	1.12E-06	Exposure → Outcome	7.10E-07
	rs4508435	G	T	7.03E-04	4.03E-07	Exposure → Outcome	9.70E-08

	rs601338	A	G	1.06E-03	2.34E-06	Exposure → Outcome	1.72E-10
	rs605093	T	G	9.10E-04	5.96E-06	Exposure → Outcome	1.10E-08
	rs60888743	G	A	1.95E-03	6.83E-07	Exposure → Outcome	3.80E-19
	rs61839660	T	C	4.91E-03	3.27E-06	Exposure → Outcome	5.03E-45
	rs61938963	T	C	4.09E-03	5.05E-08	Exposure → Outcome	1.65E-39
	rs62322711	G	A	1.30E-03	2.94E-06	Exposure → Outcome	1.96E-12
	rs6434435	A	G	6.46E-04	5.72E-08	Exposure → Outcome	2.14E-07
	rs72838204	T	C	2.90E-03	8.86E-06	Exposure → Outcome	9.31E-26
	rs72928038	A	G	1.54E-03	6.56E-08	Exposure → Outcome	1.03E-15
	rs7533782	G	A	9.42E-04	5.96E-07	Exposure → Outcome	7.08E-10
	rs77027760	A	G	8.21E-04	1.91E-06	Exposure → Outcome	1.93E-08
	rs80262450	A	G	2.04E-03	1.29E-06	Exposure → Outcome	1.06E-19
	rs8056814	A	G	2.07E-03	1.00E-05	Exposure → Outcome	2.43E-18
	rs9266642	T	C	1.95E-02	2.40E-06	Exposure → Outcome	1.83E-180

Notes: Steiger filtering was used to evaluate instrument directionality by comparing the variance explained in the exposure and outcome for each SNP. R^2_exposure > R^2_outcome indicates consistency with the assumed causal direction. Steiger test P values were interpreted as indicators of confidence in directionality.

References

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