

## Supplementary Online Content

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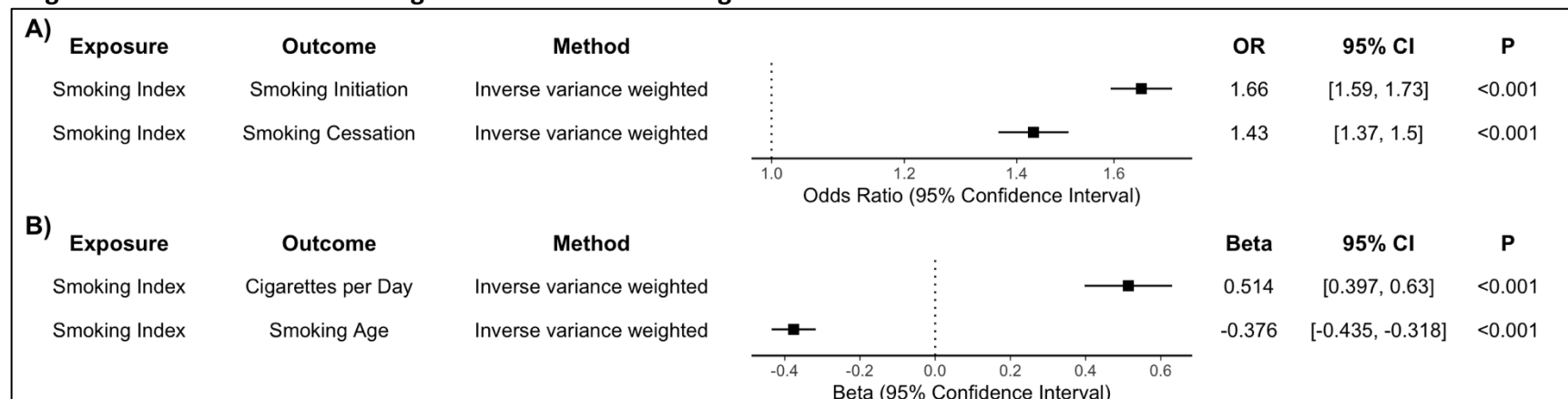
**eTable 1.** Smoking Index exposure SNPs and Corresponding SNP Effects for CAD, PAD, and Stroke Outcomes

**eTable 2.** Egger Bias Intercept Test for Smoking Index-ASCVD Analysis

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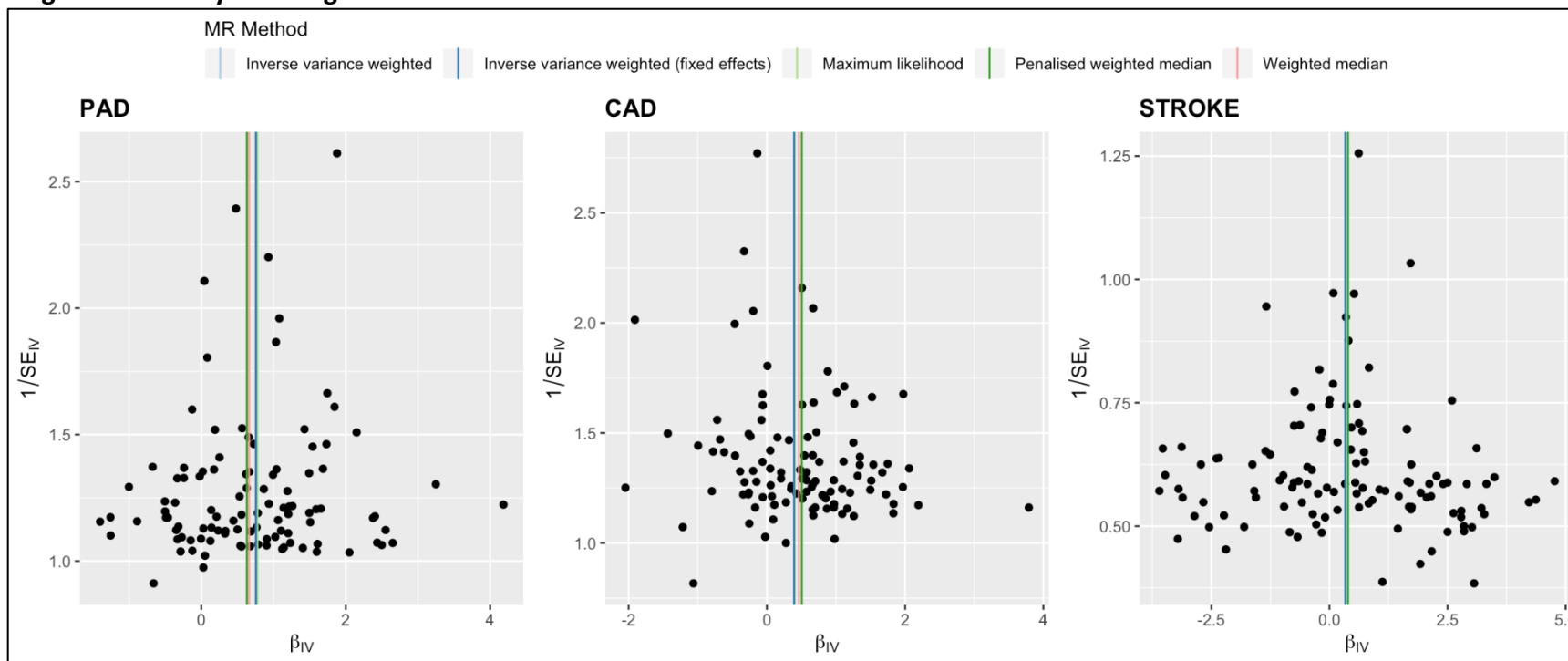
This supplementary material has been provided by the authors to give readers additional information about their work.

**eFigure 1. MR of Lifetime Smoking Index to GSCAN Smoking Traits**



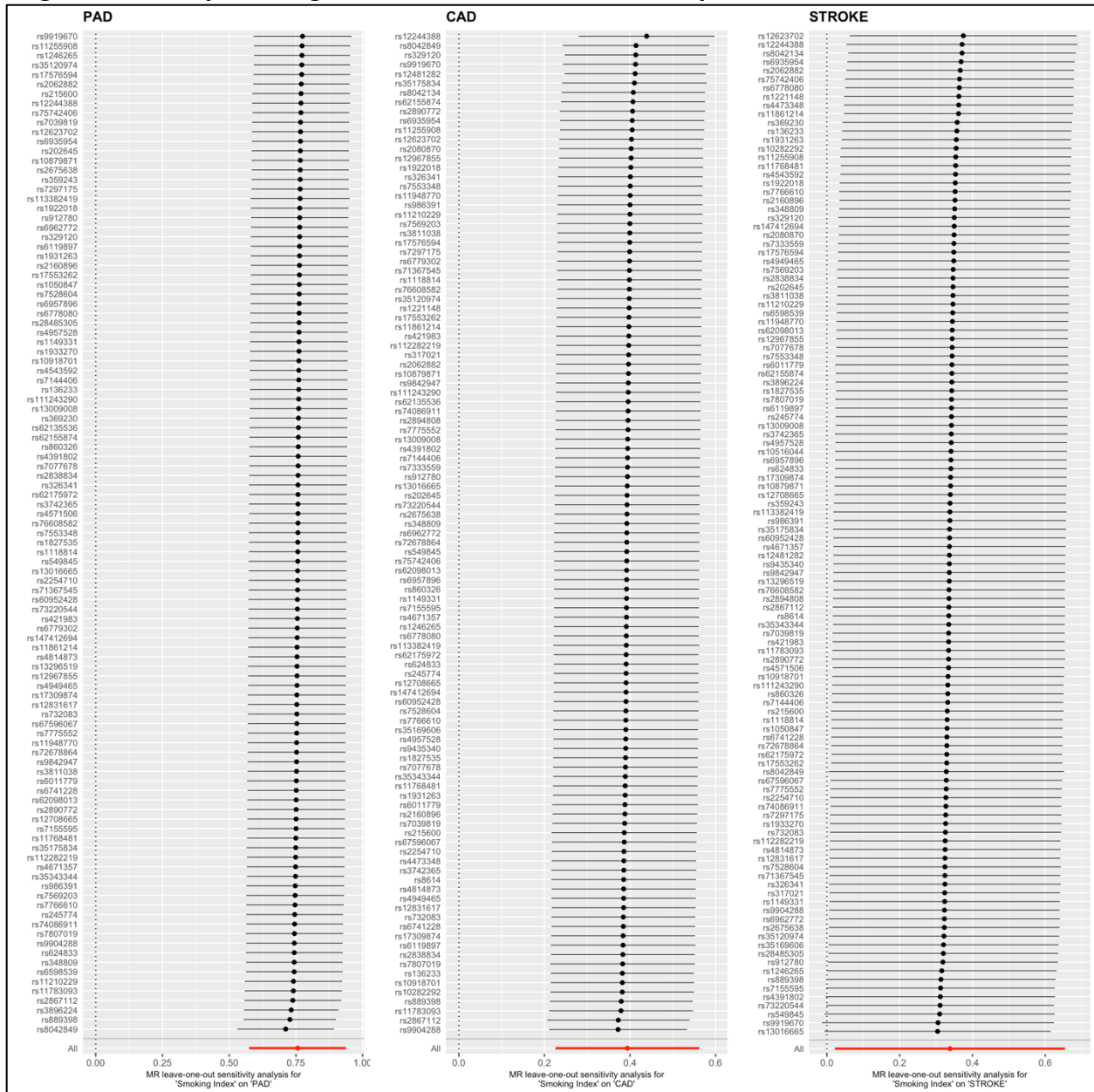
The lifetime smoking instrument was validated against smoking exposures from the GSCAN consortium. A) Odds ratios for the effect of each one standard deviation increase in lifetime smoking on Smoking Initiation and Smoking Cessation. B) Beta coefficients for the effect of each one standard deviation increase in lifetime smoking on Cigarettes per Day and Smoking Age (age of initiation). OR = Odds Ratio, CI = Confidence Interval.

**eFigure 2. Primary Smoking-ASCVD MR Funnel Plots**



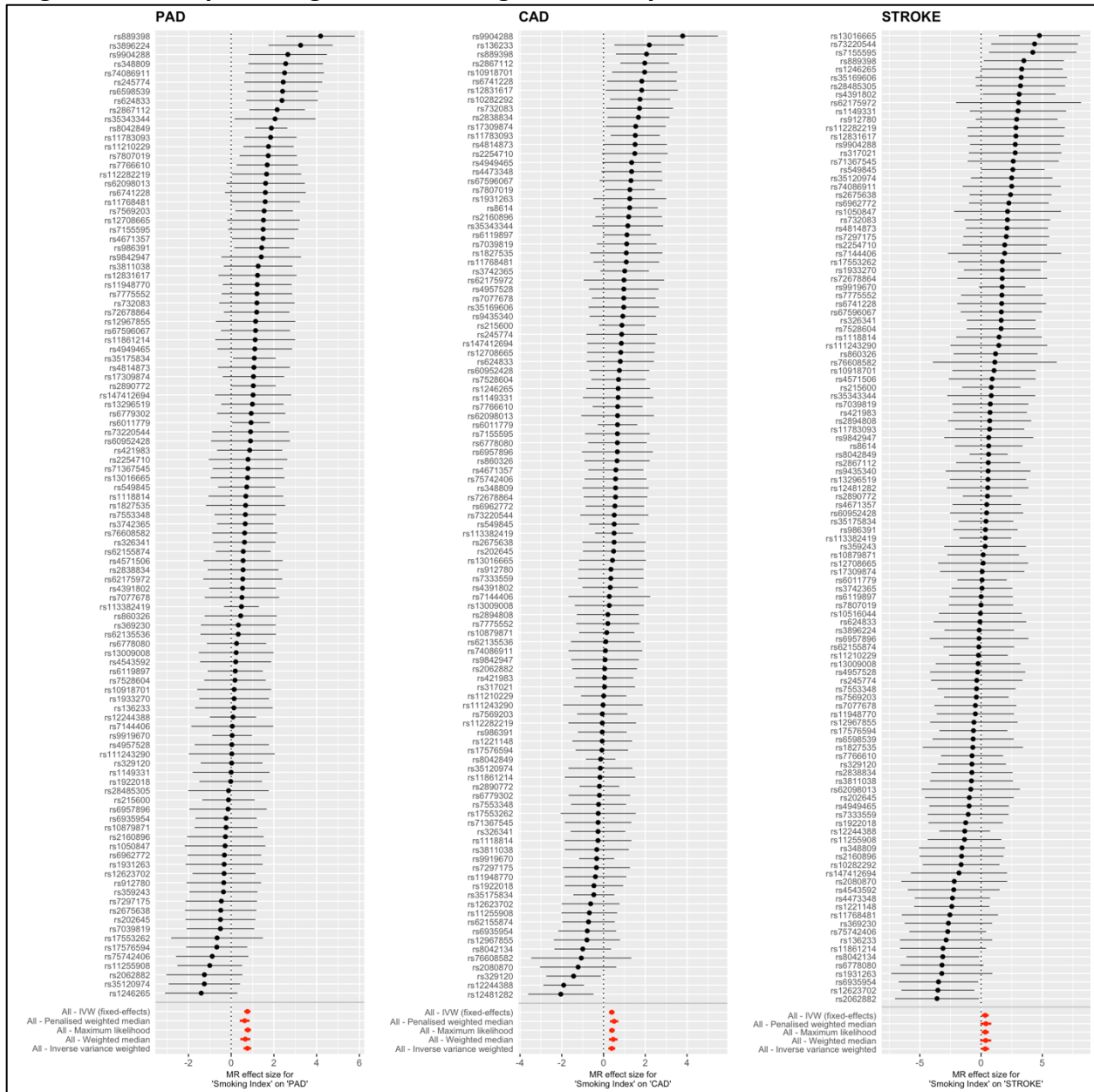
Funnel plots showing the relationship between the SNP-level causal effects of lifetime smoking index on each ASCVD outcome (PAD, CAD, and large artery stroke) against the inverse of the standard error of the causal estimate. Vertical lines represent the MR estimates using all SNPs for each of five different MR methods. Asymmetry in funnel plots may be an indicator of heterogeneous effects that may be related to directional horizontal pleiotropy or “winner’s curse” that lead to bias in effect estimates.

eFigure 3. Primary Smoking-ASCVD MR Leave-One-Out Analysis



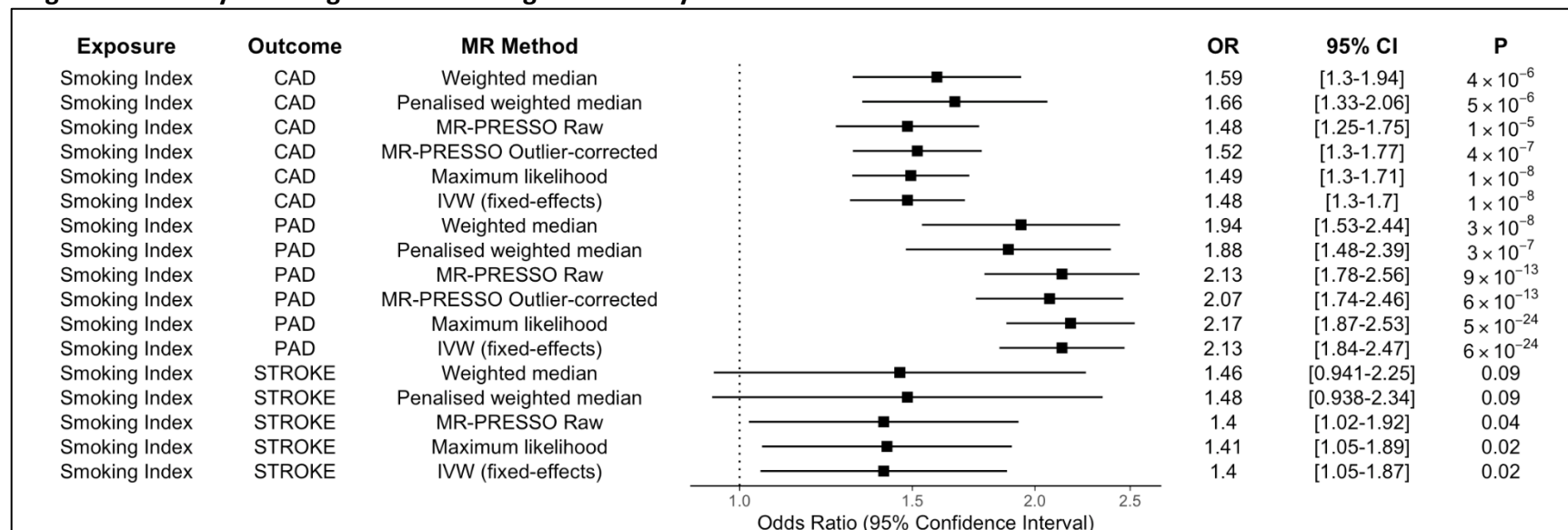
In leave-one-out analysis, each individual SNP is sequentially excluded from the inverse variance weighted MR model to identify outlier SNPs that may drive outside effects. Plotted are the log odds ratios of each leave-one-out model for each ASCVD outcome (CAD, PAD, and large artery stroke) against the SNP excluded from each model. Lines extending from each point represent the 95% confidence intervals of the effect estimate.

eFigure 4. Primary Smoking-ASCVD MR Single-SNP Analysis



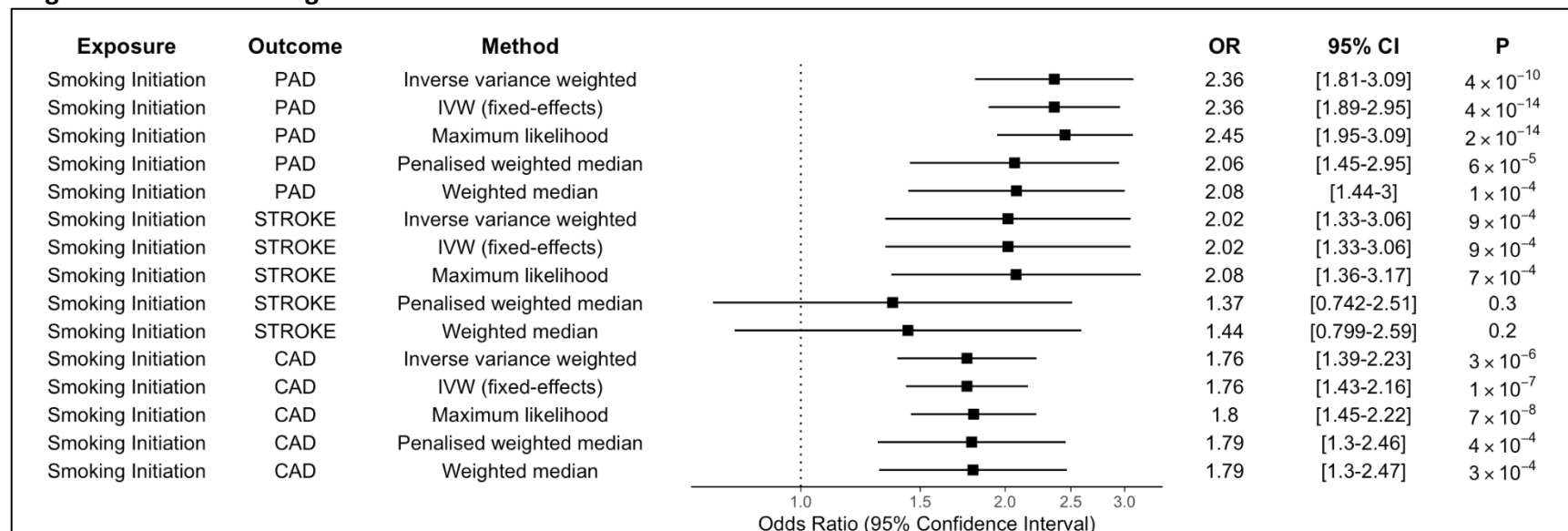
The single-SNP MR method plots the Wald estimate of the effect of each SNP included in the lifetime smoking genetic instrument on each ASCVD outcome. Lines extending from each point represent the 95% confidence interval of the odds ratio (points). Red estimates at the bottom of each plot represent the summary measures from five MR models including all of the individual SNPs.

**eFigure 5. Primary Smoking-ASCVD MR Single-SNP Analysis**



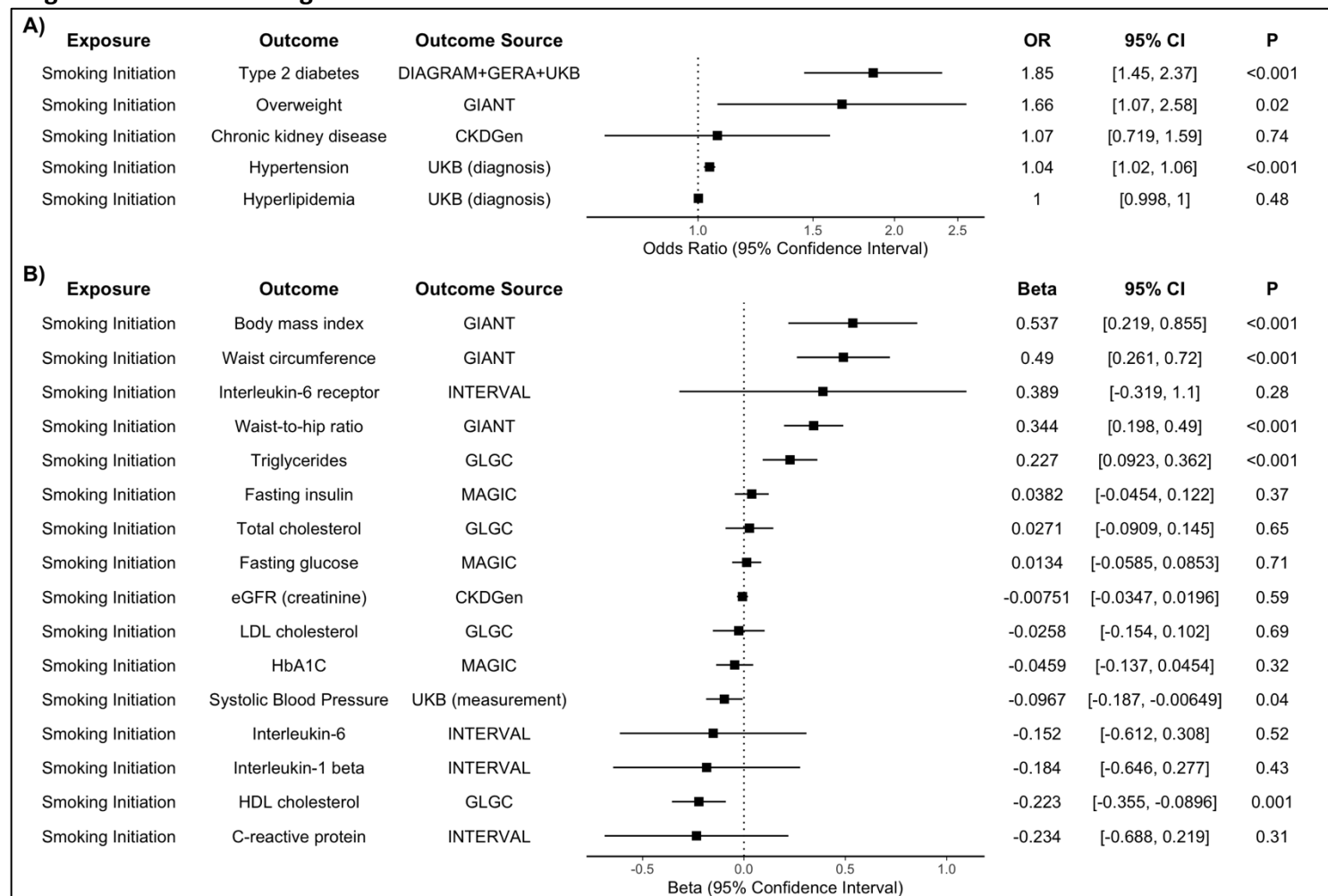
The effect of each one standard deviation increase in lifetime smoking index on each ASCVD outcome (CAD, PAD, and large artery stroke) was estimated using multiple MR methods that make different assumptions about the potential violations of the instrumental variable assumptions, heterogeneity, and error in the instrument-exposure associations. The effect of smoking on each outcome was consistent across MR models.

**eFigure 6. MR of Smoking Initiation to ASCVD Outcomes**



The robustness of the effect of lifetime smoking on ASCVD outcomes was assessed using an additional genetic instrument for smoking (Smoking Initiation). The effect of each one standard deviation increase in smoking initiation on each ASCVD outcome (CAD, PAD, and large artery stroke) was estimated using multiple MR methods that make different assumptions about the potential violations of the instrumental variable assumptions, heterogeneity, and error in the instrument-exposure associations.

**eFigure 7. MR of Smoking Initiation to Cardiometabolic Risk Factors**



The robustness of the effect of lifetime smoking on cardiometabolic outcomes was assessed using an additional genetic instrument for smoking (Smoking Initiation). The effect of each one standard deviation increase in smoking initiation on each cardiometabolic outcome (CAD, PAD, and large artery stroke) was estimated using inverse variance weighted MR. Genetic liability to smoking increased risk of both **(A)** binary traits, and **(B)** continuous traits that are common risk factors for cardiometabolic disease. OR = Odds Ratio, CI = Confidence Interval.



**eTable 1. Smoking Index exposure SNPs and Corresponding SNP Effects for CAD, PAD, and Stroke Outcomes**

Exposure	Outcome	SNP	Effect allele	Alternate allele	EAF exposure	Beta exposure	SE exposure	P exposure	Beta outcome	SE outcome	P outcome
Smoking Index	PAD	rs1050847	C	T	0.426	0.011	0.002	1.80E-08	-0.003166	0.0106	0.7651
Smoking Index	PAD	rs10879871	T	G	0.343	-0.014	0.002	5.60E-11	0.003389	0.01054	0.7479
Smoking Index	PAD	rs10918701	G	A	0.372	0.012	0.002	2.00E-08	0.00169	0.0106	0.8734
Smoking Index	PAD	rs111243290	T	C	0.963	-0.029	0.005	4.30E-08	-0.00081	0.02976	0.9783
Smoking Index	PAD	rs1118814	G	A	0.324	0.012	0.002	1.40E-08	0.008215	0.01074	0.4446
Smoking Index	PAD	rs11210229	A	G	0.384	0.017	0.002	2.80E-16	0.02966	0.01022	0.003727
Smoking Index	PAD	rs112282219	G	A	0.959	-0.033	0.005	3.70E-11	-0.05464	0.02734	0.04676
Smoking Index	PAD	rs11255908	T	G	0.743	-0.015	0.002	1.90E-10	0.01505	0.0116	0.194
Smoking Index	PAD	rs113382419	C	A	0.889	-0.041	0.003	9.70E-38	-0.01966	0.01713	0.2519
Smoking Index	PAD	rs1149331	G	A	0.477	-0.011	0.002	3.20E-08	0.00005096	0.01011	0.996
Smoking Index	PAD	rs11768481	C	A	0.666	0.013	0.002	1.00E-09	0.02067	0.01079	0.05516
Smoking Index	PAD	rs11783093	C	T	0.839	0.023	0.003	1.00E-16	0.04243	0.01429	0.002903
Smoking Index	PAD	rs11861214	G	T	0.784	0.013	0.002	2.60E-08	0.01457	0.01241	0.24
Smoking Index	PAD	rs11948770	T	C	0.768	-0.015	0.002	4.00E-10	-0.01825	0.01234	0.1393
Smoking Index	PAD	rs12244388	G	A	0.661	-0.019	0.002	9.60E-20	-0.001552	0.01053	0.8829
Smoking Index	PAD	rs1246265	T	C	0.305	-0.013	0.002	5.30E-09	0.01824	0.01125	0.1051
Smoking Index	PAD	rs12623702	A	G	0.613	-0.014	0.002	5.70E-12	0.004671	0.01055	0.6578
Smoking Index	PAD	rs12708665	A	G	0.285	-0.013	0.002	3.40E-09	-0.01961	0.01127	0.08163

Smoking Index	PAD	rs12831617	C	T	0.764	-0.013	0.002	2.40E-08	-0.01601	0.01213	0.1872
Smoking Index	PAD	rs12967855	A	G	0.331	0.012	0.002	4.00E-08	0.0137	0.01139	0.2295
Smoking Index	PAD	rs13009008	A	G	0.328	0.012	0.002	6.40E-09	0.002786	0.01071	0.7948
Smoking Index	PAD	rs13016665	C	A	0.577	-0.012	0.002	1.40E-09	-0.009174	0.01059	0.3866
Smoking Index	PAD	rs13296519	G	T	0.606	-0.014	0.002	1.40E-11	-0.0139	0.01044	0.1831
Smoking Index	PAD	rs136233	A	G	0.809	-0.014	0.003	2.70E-08	-0.001754	0.01297	0.8924
Smoking Index	PAD	rs147412694	G	A	0.85	-0.017	0.003	2.30E-09	-0.0174	0.01552	0.2629
Smoking Index	PAD	rs17309874	G	A	0.74	-0.016	0.002	5.60E-13	-0.01666	0.01174	0.1561
Smoking Index	PAD	rs17553262	A	C	0.885	-0.018	0.003	6.90E-09	0.01191	0.01974	0.546
Smoking Index	PAD	rs17576594	G	A	0.724	0.016	0.002	1.90E-12	-0.0108	0.01166	0.3548
Smoking Index	PAD	rs1827535	T	G	0.686	-0.012	0.002	1.20E-08	-0.008078	0.01134	0.4764
Smoking Index	PAD	rs1922018	C	T	0.364	0.014	0.002	2.50E-12	-0.0003203	0.01049	0.9757
Smoking Index	PAD	rs1931263	G	T	0.51	-0.011	0.002	4.00E-08	0.003646	0.01013	0.7189
Smoking Index	PAD	rs1933270	T	G	0.364	0.013	0.002	1.70E-10	0.00178	0.01082	0.8694
Smoking Index	PAD	rs202645	A	G	0.203	-0.015	0.002	5.00E-09	0.007542	0.01254	0.5478
Smoking Index	PAD	rs2062882	G	A	0.587	-0.012	0.002	1.00E-08	0.01507	0.0109	0.1668
Smoking Index	PAD	rs215600	G	A	0.358	0.017	0.002	2.00E-15	-0.002176	0.01063	0.8378
Smoking Index	PAD	rs2160896	C	T	0.317	-0.012	0.002	2.20E-08	0.003263	0.01097	0.7662
Smoking Index	PAD	rs2254710	C	A	0.236	0.013	0.002	3.00E-08	0.01022	0.0122	0.4026
Smoking Index	PAD	rs245774	A	G	0.272	-0.013	0.002	9.00E-09	-0.03165	0.01212	0.008915
Smoking Index	PAD	rs2675638	G	A	0.581	0.012	0.002	1.20E-09	-0.005877	0.01024	0.5661
Smoking Index	PAD	rs2838834	C	T	0.699	-0.013	0.002	9.20E-10	-0.00723	0.01099	0.5108
Smoking Index	PAD	rs28485305	C	T	0.631	0.011	0.002	2.80E-08	-0.001375	0.01057	0.8965
Smoking Index	PAD	rs2867112	T	G	0.835	0.021	0.003	8.30E-15	0.04515	0.01392	0.001137
Smoking Index	PAD	rs2890772	G	T	0.413	-0.02	0.002	3.60E-22	-0.02068	0.01072	0.05367

Smoking Index	PAD	rs326341	G	A	0.525	0.014	0.002	8.70E-12	0.008683	0.01042	0.4048
Smoking Index	PAD	rs329120	C	T	0.581	0.014	0.002	5.80E-12	0.0002788	0.01034	0.9785
Smoking Index	PAD	rs348809	A	G	0.348	-0.012	0.002	1.90E-08	-0.03062	0.01069	0.004137
Smoking Index	PAD	rs35120974	A	G	0.583	-0.012	0.002	2.10E-09	0.0151	0.01023	0.1397
Smoking Index	PAD	rs35175834	G	A	0.788	-0.024	0.002	4.80E-22	-0.02592	0.01225	0.0346
Smoking Index	PAD	rs35343344	C	A	0.733	0.013	0.002	1.00E-08	0.02666	0.01257	0.03366
Smoking Index	PAD	rs359243	T	C	0.393	-0.013	0.002	8.30E-10	0.00472	0.01056	0.655
Smoking Index	PAD	rs369230	G	T	0.308	-0.013	0.002	2.00E-09	-0.004333	0.01162	0.7092
Smoking Index	PAD	rs3742365	T	C	0.595	-0.016	0.002	2.30E-14	-0.01048	0.01074	0.3294
Smoking Index	PAD	rs3811038	T	C	0.724	-0.014	0.002	9.20E-10	-0.01765	0.0115	0.1252
Smoking Index	PAD	rs3896224	A	G	0.585	0.014	0.002	1.00E-11	0.04547	0.01074	0.00002261
Smoking Index	PAD	rs421983	T	C	0.519	0.013	0.002	3.10E-10	0.01124	0.01012	0.2664
Smoking Index	PAD	rs4391802	A	G	0.707	0.015	0.002	1.30E-11	0.007948	0.01195	0.5059
Smoking Index	PAD	rs4543592	T	C	0.52	-0.012	0.002	4.90E-10	-0.002519	0.01021	0.8052
Smoking Index	PAD	rs4571506	C	T	0.54	0.011	0.002	1.60E-08	0.006118	0.0104	0.5563
Smoking Index	PAD	rs4671357	T	C	0.519	-0.014	0.002	1.10E-11	-0.0209	0.01039	0.04428
Smoking Index	PAD	rs4814873	C	T	0.767	0.014	0.002	2.70E-09	0.01488	0.01205	0.2168
Smoking Index	PAD	rs4949465	T	C	0.87	-0.017	0.003	1.50E-08	-0.01876	0.01518	0.2171
Smoking Index	PAD	rs4957528	A	C	0.208	-0.015	0.002	4.50E-09	-0.000419	0.01329	0.9748
Smoking Index	PAD	rs549845	G	A	0.301	0.016	0.002	9.90E-14	0.01163	0.01094	0.2883
Smoking Index	PAD	rs6011779	C	T	0.191	0.028	0.003	1.60E-27	0.026	0.01272	0.04133
Smoking Index	PAD	rs60952428	T	C	0.909	0.019	0.003	3.40E-08	0.01718	0.0179	0.3363
Smoking Index	PAD	rs6119897	G	A	0.762	-0.018	0.002	3.10E-15	-0.003401	0.01185	0.7741
Smoking Index	PAD	rs62098013	G	A	0.64	-0.012	0.002	5.60E-09	-0.01932	0.01124	0.08583
Smoking Index	PAD	rs62135536	C	T	0.968	0.035	0.006	6.80E-10	0.01148	0.03157	0.7159
Smoking Index	PAD	rs62155874	A	G	0.873	-0.024	0.003	4.00E-16	-0.01355	0.01574	0.3898
Smoking Index	PAD	rs62175972	T	C	0.966	0.031	0.006	1.70E-08	0.01678	0.02923	0.5651

Smoking Index	PAD	rs624833	T	G	0.695	0.013	0.002	9.20E-10	0.0309	0.01111	0.005333
Smoking Index	PAD	rs6598539	T	C	0.489	-0.012	0.002	3.70E-09	-0.02884	0.0102	0.004695
Smoking Index	PAD	rs6741228	T	C	0.433	0.011	0.002	1.70E-08	0.01758	0.01061	0.09752
Smoking Index	PAD	rs6759606 7	G	A	0.649	-0.013	0.002	1.10E-09	-0.01481	0.01074	0.168
Smoking Index	PAD	rs6778080	T	C	0.267	0.016	0.002	2.10E-12	0.004017	0.01135	0.7235
Smoking Index	PAD	rs6779302	G	T	0.633	-0.013	0.002	1.40E-09	-0.01217	0.0106	0.2513
Smoking Index	PAD	rs6935954	A	G	0.421	0.014	0.002	9.60E-12	-0.003373	0.01023	0.7416
Smoking Index	PAD	rs6957896	C	T	0.503	-0.011	0.002	1.90E-08	0.001631	0.01017	0.8726
Smoking Index	PAD	rs6962772	A	G	0.846	0.016	0.003	8.60E-09	-0.005086	0.01408	0.718
Smoking Index	PAD	rs7039819	G	A	0.427	0.013	0.002	5.20E-10	-0.006572	0.01052	0.5323
Smoking Index	PAD	rs7077678	C	T	0.623	0.012	0.002	2.40E-09	0.006004	0.01067	0.5737
Smoking Index	PAD	rs7136754 5	G	A	0.791	-0.015	0.002	1.70E-09	-0.01171	0.01261	0.3534
Smoking Index	PAD	rs7144406	A	G	0.791	-0.013	0.002	4.20E-08	- 0.000652 5	0.01273	0.9591
Smoking Index	PAD	rs7155595	A	C	0.674	-0.013	0.002	3.40E-09	-0.01944	0.01092	0.07521
Smoking Index	PAD	rs7267886 4	G	A	0.829	0.018	0.003	1.70E-11	0.02147	0.0141	0.1272
Smoking Index	PAD	rs7297175	T	C	0.431	-0.012	0.002	1.10E-08	0.005548	0.01024	0.5881
Smoking Index	PAD	rs732083	G	A	0.333	0.012	0.002	1.40E-08	0.01443	0.01081	0.1823
Smoking Index	PAD	rs7322054 4	A	C	0.842	-0.016	0.003	1.50E-08	-0.01451	0.01472	0.3248
Smoking Index	PAD	rs7408691 1	G	A	0.925	0.021	0.004	2.00E-08	0.05246	0.01975	0.007594
Smoking Index	PAD	rs7528604	G	A	0.566	0.014	0.002	6.60E-12	0.002456	0.01028	0.8112
Smoking Index	PAD	rs7553348	G	A	0.438	0.014	0.002	5.90E-12	0.009282	0.01035	0.3697
Smoking Index	PAD	rs7569203	A	C	0.689	-0.016	0.002	5.50E-13	-0.02465	0.01102	0.02543
Smoking Index	PAD	rs7574240 6	G	A	0.739	0.014	0.002	1.20E-09	-0.01245	0.0121	0.3042
Smoking Index	PAD	rs7660858 2	C	A	0.953	0.031	0.005	3.40E-10	0.01947	0.02406	0.4175
Smoking Index	PAD	rs7766610	C	A	0.183	0.018	0.003	2.40E-12	0.03032	0.01319	0.02173
Smoking Index	PAD	rs7775552	A	G	0.513	-1.20E-02	0.002	2.50E-09	-0.01445	0.01012	0.1533
Smoking Index	PAD	rs7807019	A	G	0.54	-0.015	0.002	7.50E-14	-0.02599	0.01026	0.01131
Smoking Index	PAD	rs8042849	C	T	0.342	2.80E-02	0.002	2.40E-39	0.05263	0.01072	9.38E-07

Smoking Index	PAD	rs860326	C	T	0.428	0.012	0.002	3.20E-09	0.005334	0.01035	0.6064
Smoking Index	PAD	rs889398	C	T	0.588	0.013	0.002	3.90E-11	0.05439	0.01063	3.04E-07
Smoking Index	PAD	rs912780	T	G	0.65	0.012	0.002	8.50E-09	-0.004179	0.01069	0.696
Smoking Index	PAD	rs9842947	C	T	0.326	-0.012	0.002	4.40E-09	-0.01687	0.01141	0.1391
Smoking Index	PAD	rs986391	G	A	0.367	0.016	0.002	1.30E-14	0.02285	0.01052	0.02987
Smoking Index	PAD	rs9904288	T	C	0.708	0.012	0.002	2.40E-08	0.0318	0.0112	0.004475
Smoking Index	PAD	rs9919670	G	A	0.612	-0.022	0.002	2.10E-26	- 0.000918 2	0.01044	0.9299
Smoking Index	STROK E	rs1028229 2	C	T	0.362	0.013	0.002	7.10E-10	-0.0212	0.0208	0.3068
Smoking Index	STROK E	rs1050847	C	T	0.426	0.011	0.002	1.80E-08	0.0238	0.0245	0.3316
Smoking Index	STROK E	rs1051604 4	G	C	0.884	-0.02	0.003	2.00E-10	0.0011	0.0346	0.9754
Smoking Index	STROK E	rs1087987 1	T	G	0.343	-0.014	0.002	5.60E-11	-0.0024	0.0209	0.9078
Smoking Index	STROK E	rs1091870 1	G	A	0.372	0.012	0.002	2.00E-08	0.0127	0.0209	0.5439
Smoking Index	STROK E	rs1112432 90	T	C	0.963	-0.029	0.005	4.30E-08	-0.042	0.0586	0.4735
Smoking Index	STROK E	rs1118814	G	A	0.324	0.012	0.002	1.40E-08	0.0176	0.0214	0.4099
Smoking Index	STROK E	rs1121022 9	A	G	0.384	0.017	0.002	2.80E-16	-0.0036	0.0208	0.8638
Smoking Index	STROK E	rs1122822 19	G	A	0.959	-0.033	0.005	3.70E-11	-0.094	0.0674	0.1631
Smoking Index	STROK E	rs1125590 8	T	G	0.743	-0.015	0.002	1.90E-10	0.0203	0.023	0.3767
Smoking Index	STROK E	rs1133824 19	C	A	0.889	-0.041	0.003	9.70E-38	-0.0143	0.0444	0.7474
Smoking Index	STROK E	rs1149331	G	A	0.477	-0.011	0.002	3.20E-08	-0.0332	0.0221	0.1327
Smoking Index	STROK E	rs1176848 1	C	A	0.666	0.013	0.002	1.00E-09	-0.0331	0.0261	0.2044
Smoking Index	STROK E	rs1178309 3	C	T	0.839	0.023	0.003	1.00E-16	0.016	0.0332	0.6306

Smoking Index	STROKE	rs11861214	G	T	0.784	0.013	0.002	2.60E-08	-0.0404	0.0233	0.0821997
Smoking Index	STROKE	rs11948770	T	C	0.768	-0.015	0.002	4.00E-10	0.007	0.0242	0.7718
Smoking Index	STROKE	rs1221148	C	G	0.587	0.013	0.002	4.60E-11	-0.0311	0.0204	0.1271
Smoking Index	STROKE	rs12244388	G	A	0.661	-0.019	0.002	9.60E-20	0.0254	0.0201	0.2059
Smoking Index	STROKE	rs1246265	T	C	0.305	-0.013	0.002	5.30E-09	-0.0432	0.0222	0.0516904
Smoking Index	STROKE	rs12481282	G	C	0.722	-0.013	0.002	7.80E-09	-0.0071	0.0221	0.75
Smoking Index	STROKE	rs12623702	A	G	0.613	-0.014	0.002	5.70E-12	0.0494	0.0213	0.0203498
Smoking Index	STROKE	rs12708665	A	G	0.285	-0.013	0.002	3.40E-09	-0.0022	0.0244	0.9292
Smoking Index	STROKE	rs12831617	C	T	0.764	-0.013	0.002	2.40E-08	-0.037	0.026	0.1548
Smoking Index	STROKE	rs12967855	A	G	0.331	0.012	0.002	4.00E-08	-0.007	0.0219	0.7485
Smoking Index	STROKE	rs13009008	A	G	0.328	0.012	0.002	6.40E-09	-0.0029	0.0212	0.8921
Smoking Index	STROKE	rs13016665	C	A	0.577	-0.012	0.002	1.40E-09	-0.0572	0.0203	0.00487697
Smoking Index	STROKE	rs13296519	G	T	0.606	-0.014	0.002	1.40E-11	-0.0079	0.0223	0.725
Smoking Index	STROKE	rs136233	A	G	0.809	-0.014	0.003	2.70E-08	0.04	0.0269	0.1369
Smoking Index	STROKE	rs147412694	G	A	0.85	-0.017	0.003	2.30E-09	0.0307	0.0341	0.3687
Smoking Index	STROKE	rs17309874	G	A	0.74	-0.016	0.002	5.60E-13	-0.0015	0.0281	0.9568
Smoking Index	STROKE	rs17553262	A	C	0.885	-0.018	0.003	6.90E-09	-0.0313	0.0334	0.3484
Smoking Index	STROKE	rs17576594	G	A	0.724	0.016	0.002	1.90E-12	-0.01	0.0227	0.6607

Smoking Index	STROK E	rs1827535	T	G	0.686	-0.012	0.002	1.20E-08	0.0081	0.0251	0.7462
Smoking Index	STROK E	rs1922018	C	T	0.364	0.014	0.002	2.50E-12	-0.0176	0.0217	0.4157
Smoking Index	STROK E	rs1931263	G	T	0.51	-0.011	0.002	4.00E-08	0.0353	0.0232	0.1277
Smoking Index	STROK E	rs1933270	T	G	0.364	0.013	0.002	1.70E-10	0.0225	0.0208	0.2781
Smoking Index	STROK E	rs202645	A	G	0.203	-0.015	0.002	5.00E-09	0.0144	0.0278	0.6052
Smoking Index	STROK E	rs2062882	G	A	0.587	-0.012	0.002	1.00E-08	0.0432	0.021	0.039720 1
Smoking Index	STROK E	rs2080870	A	T	0.258	0.012	0.002	4.50E-08	-0.0263	0.0265	0.3219
Smoking Index	STROK E	rs215600	G	A	0.358	0.017	0.002	2.00E-15	0.0142	0.0207	0.4932
Smoking Index	STROK E	rs2160896	C	T	0.317	-0.012	0.002	2.20E-08	0.0191	0.021	0.365
Smoking Index	STROK E	rs2254710	C	A	0.236	0.013	0.002	3.00E-08	0.0251	0.0229	0.272
Smoking Index	STROK E	rs245774	A	G	0.272	-0.013	0.002	9.00E-09	0.0046	0.0248	0.8523
Smoking Index	STROK E	rs2675638	G	A	0.581	0.012	0.002	1.20E-09	0.0289	0.0205	0.1573
Smoking Index	STROK E	rs2838834	C	T	0.699	-0.013	0.002	9.20E-10	0.0098	0.0221	0.6584
Smoking Index	STROK E	rs2848530 5	C	T	0.631	0.011	0.002	2.80E-08	0.0354	0.0205	0.084009 8
Smoking Index	STROK E	rs2867112	T	G	0.835	0.021	0.003	8.30E-15	0.0123	0.0281	0.662599
Smoking Index	STROK E	rs2890772	G	T	0.413	-0.02	0.002	3.60E-22	-0.0104	0.0206	0.6132
Smoking Index	STROK E	rs2894808	T	A	0.922	-0.022	0.004	4.50E-09	-0.0155	0.0381	0.6831
Smoking Index	STROK E	rs317021	T	A	0.814	-0.017	0.003	6.80E-11	-0.0474	0.0328	0.148

Smoking Index	STROKE	rs326341	G	A	0.525	0.014	0.002	8.70E-12	0.023	0.0201	0.2525
Smoking Index	STROKE	rs329120	C	T	0.581	0.014	0.002	5.80E-12	-0.0105	0.0199	0.5975
Smoking Index	STROKE	rs348809	A	G	0.348	-0.012	0.002	1.90E-08	0.0187	0.0215	0.3856
Smoking Index	STROKE	rs35120974	A	G	0.583	-0.012	0.002	2.10E-09	-0.03	0.0204	0.1415
Smoking Index	STROKE	rs35169606	T	G	0.612	0.013	0.002	1.20E-09	0.0426	0.0248	0.0860796
Smoking Index	STROKE	rs35175834	G	A	0.788	-0.024	0.002	4.80E-22	-0.0096	0.0274	0.7259
Smoking Index	STROKE	rs35343344	C	A	0.733	0.013	0.002	1.00E-08	0.0108	0.0238	0.6511
Smoking Index	STROKE	rs359243	T	C	0.393	-0.013	0.002	8.30E-10	-0.0043	0.0222	0.8453
Smoking Index	STROKE	rs369230	G	T	0.308	-0.013	0.002	2.00E-09	0.0347	0.0237	0.1434
Smoking Index	STROKE	rs3742365	T	C	0.595	-0.016	0.002	2.30E-14	-0.0012	0.0203	0.9539
Smoking Index	STROKE	rs3811038	T	C	0.724	-0.014	0.002	9.20E-10	0.011	0.0242	0.649999
Smoking Index	STROKE	rs3896224	A	G	0.585	0.014	0.002	1.00E-11	-0.0021	0.0203	0.9177
Smoking Index	STROKE	rs421983	T	C	0.519	0.013	0.002	3.10E-10	0.0095	0.02	0.6351
Smoking Index	STROKE	rs4391802	A	G	0.707	0.015	0.002	1.30E-11	0.0467	0.0228	0.0405098
Smoking Index	STROKE	rs4473348	A	T	0.25	-0.015	0.002	9.00E-11	0.0351	0.0235	0.135
Smoking Index	STROKE	rs4543592	T	C	0.52	-0.012	0.002	4.90E-10	0.0268	0.023	0.2449
Smoking Index	STROKE	rs4571506	C	T	0.54	0.011	0.002	1.60E-08	0.01	0.0199	0.614601
Smoking Index	STROKE	rs4671357	T	C	0.519	-0.014	0.002	1.10E-11	-0.0065	0.02	0.743901



Smoking Index	STROKE	rs4814873	C	T	0.767	0.014	0.002	2.70E-09	0.0296	0.0239	0.2157
Smoking Index	STROKE	rs4949465	T	C	0.87	-0.017	0.003	1.50E-08	0.0166	0.0282	0.5562
Smoking Index	STROKE	rs4957528	A	C	0.208	-0.015	0.002	4.50E-09	0.0042	0.0298	0.8883
Smoking Index	STROKE	rs549845	G	A	0.301	0.016	0.002	9.90E-14	0.0415	0.0212	0.0503999
Smoking Index	STROKE	rs6011779	C	T	0.191	0.028	0.003	1.60E-27	0.0023	0.0288	0.9365
Smoking Index	STROKE	rs60952428	T	C	0.909	0.019	0.003	3.40E-08	0.0086	0.029	0.7663
Smoking Index	STROKE	rs6119897	G	A	0.762	-0.018	0.002	3.10E-15	-0.0001	0.0238	0.9968
Smoking Index	STROKE	rs62098013	G	A	0.64	-0.012	0.002	5.60E-09	0.0101	0.0246	0.6806
Smoking Index	STROKE	rs62155874	A	G	0.873	-0.024	0.003	4.00E-16	0.0044	0.0354	0.9009
Smoking Index	STROKE	rs62175972	T	C	0.966	0.031	0.006	1.70E-08	0.0949	0.0807	0.2399
Smoking Index	STROKE	rs624833	T	G	0.695	0.013	0.002	9.20E-10	-0.0012	0.0251	0.9629
Smoking Index	STROKE	rs6598539	T	C	0.489	-0.012	0.002	3.70E-09	0.0078	0.0203	0.701601
Smoking Index	STROKE	rs6741228	T	C	0.433	0.011	0.002	1.70E-08	0.0185	0.0204	0.3656
Smoking Index	STROKE	rs67596067	G	A	0.649	-0.013	0.002	1.10E-09	-0.0215	0.022	0.328
Smoking Index	STROKE	rs6778080	T	C	0.267	0.016	0.002	2.10E-12	-0.0511	0.0278	0.0665197
Smoking Index	STROKE	rs6935954	A	G	0.421	0.014	0.002	9.60E-12	-0.0487	0.0232	0.0361901
Smoking Index	STROKE	rs6957896	C	T	0.503	-0.011	0.002	1.90E-08	0.0018	0.0226	0.9351
Smoking Index	STROKE	rs6962772	A	G	0.846	0.016	0.003	8.60E-09	0.0363	0.0266	0.173

Smoking Index	STROK E	rs7039819	G	A	0.427	0.013	0.002	5.20E-10	0.0098	0.0206	0.632501
Smoking Index	STROK E	rs7077678	C	T	0.623	0.012	0.002	2.40E-09	-0.0056	0.0205	0.785301
Smoking Index	STROK E	rs7136754 5	G	A	0.791	-0.015	0.002	1.70E-09	-0.0394	0.0285	0.167
Smoking Index	STROK E	rs7144406	A	G	0.791	-0.013	0.002	4.20E-08	-0.025	0.0307	0.4156
Smoking Index	STROK E	rs7155595	A	C	0.674	-0.013	0.002	3.40E-09	-0.0549	0.0237	0.020300 2
Smoking Index	STROK E	rs7267886 4	G	A	0.829	0.018	0.003	1.70E-11	0.0311	0.0337	0.356
Smoking Index	STROK E	rs7297175	T	C	0.431	-0.012	0.002	1.10E-08	-0.0247	0.0215	0.2517
Smoking Index	STROK E	rs732083	G	A	0.333	0.012	0.002	1.40E-08	0.0258	0.0214	0.2281
Smoking Index	STROK E	rs7322054 4	A	C	0.842	-0.016	0.003	1.50E-08	-0.0699	0.0289	0.015760 1
Smoking Index	STROK E	rs7333559	G	A	0.212	0.015	0.002	5.30E-10	-0.0158	0.0253	0.531401
Smoking Index	STROK E	rs7408691 1	G	A	0.925	0.021	0.004	2.00E-08	0.0525	0.043	0.222
Smoking Index	STROK E	rs7528604	G	A	0.566	0.014	0.002	6.60E-12	0.0229	0.0201	0.2533
Smoking Index	STROK E	rs7553348	G	A	0.438	0.014	0.002	5.90E-12	-0.0052	0.0228	0.8208
Smoking Index	STROK E	rs7569203	A	C	0.689	-0.016	0.002	5.50E-13	0.0062	0.0216	0.7732
Smoking Index	STROK E	rs7574240 6	G	A	0.739	0.014	0.002	1.20E-09	-0.0381	0.0224	0.089041
Smoking Index	STROK E	rs7660858 2	C	A	0.953	0.031	0.005	3.40E-10	0.0348	0.0801	0.664
Smoking Index	STROK E	rs7766610	C	A	0.183	0.018	0.003	2.40E-12	-0.0133	0.0233	0.568
Smoking Index	STROK E	rs7775552	A	G	0.513	-0.012	0.002	2.50E-09	-0.0204	0.0204	0.317

Smoking Index	STROK E	rs7807019	A	G	0.54	-0.015	0.002	7.50E-14	0.0001	0.0201	0.9977
Smoking Index	STROK E	rs8042134	T	G	0.541	-0.014	0.002	2.20E-12	0.0438	0.0212	0.038979 8
Smoking Index	STROK E	rs8042849	C	T	0.342	0.028	0.002	2.40E-39	0.0173	0.0223	0.4364
Smoking Index	STROK E	rs860326	C	T	0.428	0.012	0.002	3.20E-09	0.0142	0.021	0.4971
Smoking Index	STROK E	rs8614	C	A	0.818	-0.017	0.003	1.50E-10	-0.0106	0.024	0.6592
Smoking Index	STROK E	rs889398	C	T	0.588	0.013	0.002	3.90E-11	0.0454	0.0217	0.036800 2
Smoking Index	STROK E	rs912780	T	G	0.65	0.012	0.002	8.50E-09	0.0349	0.0205	0.088369
Smoking Index	STROK E	rs9435340	T	A	0.344	0.012	0.002	1.00E-08	0.0069	0.0212	0.7438
Smoking Index	STROK E	rs9842947	C	T	0.326	-0.012	0.002	4.40E-09	-0.0075	0.0223	0.7364
Smoking Index	STROK E	rs986391	G	A	0.367	0.016	0.002	1.30E-14	0.0057	0.0215	0.7904
Smoking Index	STROK E	rs9904288	T	C	0.708	0.012	0.002	2.40E-08	0.0335	0.0226	0.1393
Smoking Index	STROK E	rs9919670	G	A	0.612	-0.022	0.002	2.10E-26	-0.0378	0.0213	0.076279 9
Smoking Index	CAD	rs1028229 2	C	T	0.362	0.013	0.002	7.10E-10	0.022719	0.009558 2	0.017457 8
Smoking Index	CAD	rs1087987 1	T	G	0.343	-0.014	0.002	5.60E-11	-0.002138	0.009461 5	0.821226
Smoking Index	CAD	rs1091870 1	G	A	0.372	0.012	0.002	2.00E-08	0.023604	0.009567 9	0.013625 4
Smoking Index	CAD	rs1112432 90	T	C	0.963	-0.029	0.005	4.30E-08	0.00071	0.028205 2	0.979917
Smoking Index	CAD	rs1118814	G	A	0.324	0.012	0.002	1.40E-08	-0.003204	0.009826 5	0.744381
Smoking Index	CAD	rs1121022 9	A	G	0.384	0.017	0.002	2.80E-16	0.000119	0.009420 2	0.989921

Smoking Index	CAD	rs112282219	G	A	0.959	-0.033	0.005	3.70E-11	0.001997	0.0273155	0.94172
Smoking Index	CAD	rs11255908	T	G	0.743	-0.015	0.002	1.90E-10	0.010164	0.0102002	0.319029
Smoking Index	CAD	rs113382419	C	A	0.889	-0.041	0.003	9.70E-38	-0.02074	0.0189892	0.274746
Smoking Index	CAD	rs1149331	G	A	0.477	-0.011	0.002	3.20E-08	-0.007664	0.0094702	0.418355
Smoking Index	CAD	rs11768481	C	A	0.666	0.013	0.002	1.00E-09	0.014147	0.010438	0.175312
Smoking Index	CAD	rs11783093	C	T	0.839	0.023	0.003	1.00E-16	0.034962	0.0138305	0.0114749
Smoking Index	CAD	rs11861214	G	T	0.784	0.013	0.002	2.60E-08	-0.002208	0.0111952	0.843649
Smoking Index	CAD	rs11948770	T	C	0.768	-0.015	0.002	4.00E-10	0.005828	0.011319	0.606633
Smoking Index	CAD	rs1221148	C	G	0.587	0.013	0.002	4.60E-11	-0.000828	0.0094973	0.930526
Smoking Index	CAD	rs12244388	G	A	0.661	-0.019	0.002	9.60E-20	0.036276	0.0094343	0.000120501
Smoking Index	CAD	rs1246265	T	C	0.305	-0.013	0.002	5.30E-09	-0.009105	0.0101448	0.369448
Smoking Index	CAD	rs12481282	G	C	0.722	-0.013	0.002	7.80E-09	0.026601	0.0103881	0.0104455
Smoking Index	CAD	rs12623702	A	G	0.613	-0.014	0.002	5.70E-12	0.008648	0.0099101	0.382857
Smoking Index	CAD	rs12708665	A	G	0.285	-0.013	0.002	3.40E-09	-0.010716	0.0106944	0.316334
Smoking Index	CAD	rs12831617	C	T	0.764	-0.013	0.002	2.40E-08	-0.023783	0.0114537	0.037853
Smoking Index	CAD	rs12967855	A	G	0.331	0.012	0.002	4.00E-08	-0.009557	0.0097124	0.325116
Smoking Index	CAD	rs13009008	A	G	0.328	0.012	0.002	6.40E-09	0.003304	0.0101295	0.744291
Smoking Index	CAD	rs13016665	C	A	0.577	-0.012	0.002	1.40E-09	-0.005148	0.0097971	0.599264

Smoking Index	CAD	rs136233	A	G	0.809	-0.014	0.003	2.70E-08	-0.030685	0.011942 5	0.010187 8
Smoking Index	CAD	rs1474126 94	G	A	0.85	-0.017	0.003	2.30E-09	-0.014472	0.014130 3	0.30575
Smoking Index	CAD	rs1730987 4	G	A	0.74	-0.016	0.002	5.60E-13	-0.024627	0.011799 2	0.036871 4
Smoking Index	CAD	rs1755326 2	A	C	0.885	-0.018	0.003	6.90E-09	0.004595	0.016537 5	0.781124
Smoking Index	CAD	rs1757659 4	G	A	0.724	0.016	0.002	1.90E-12	-0.001252	0.010264 2	0.902917
Smoking Index	CAD	rs1827535	T	G	0.686	-0.012	0.002	1.20E-08	-0.013067	0.010598 8	0.217623
Smoking Index	CAD	rs1922018	C	T	0.364	0.014	0.002	2.50E-12	-0.006448	0.010022	0.519974
Smoking Index	CAD	rs1931263	G	T	0.51	-0.011	0.002	4.00E-08	-0.013821	0.009799 3	0.15842
Smoking Index	CAD	rs202645	A	G	0.203	-0.015	0.002	5.00E-09	-0.00722	0.011254 9	0.5212
Smoking Index	CAD	rs2062882	G	A	0.587	-0.012	0.002	1.00E-08	-0.000649	0.009504 9	0.945562
Smoking Index	CAD	rs2080870	A	T	0.258	0.012	0.002	4.50E-08	-0.014601	0.011189 8	0.191942
Smoking Index	CAD	rs215600	G	A	0.358	0.017	0.002	2.00E-15	0.014977	0.009549 5	0.116797
Smoking Index	CAD	rs2160896	C	T	0.317	-0.012	0.002	2.20E-08	-0.01444	0.009765 6	0.139233
Smoking Index	CAD	rs2254710	C	A	0.236	0.013	0.002	3.00E-08	0.019446	0.010468 5	0.063228 1
Smoking Index	CAD	rs245774	A	G	0.272	-0.013	0.002	9.00E-09	-0.011289	0.011245 2	0.315427
Smoking Index	CAD	rs2675638	G	A	0.581	0.012	0.002	1.20E-09	0.006059	0.009276 8	0.51367
Smoking Index	CAD	rs2838834	C	T	0.699	-0.013	0.002	9.20E-10	-0.021708	0.009846	0.027472
Smoking Index	CAD	rs2867112	T	G	0.835	0.021	0.003	8.30E-15	0.041434	0.012523 7	0.000938 102
Smoking Index	CAD	rs2890772	G	T	0.413	-0.02	0.002	3.60E-22	0.003933	0.009736 3	0.686248

Smoking Index	CAD	rs2894808	T	A	0.922	-0.022	0.004	4.50E-09	-0.004522	0.016658 1	0.786037
Smoking Index	CAD	rs317021	T	A	0.814	-0.017	0.003	6.80E-11	-0.000821	0.012704	0.948472
Smoking Index	CAD	rs326341	G	A	0.525	0.014	0.002	8.70E-12	-0.003695	0.009362 6	0.693099
Smoking Index	CAD	rs329120	C	T	0.581	0.014	0.002	5.80E-12	-0.020066	0.009347 4	0.031817 8
Smoking Index	CAD	rs348809	A	G	0.348	-0.012	0.002	1.90E-08	-0.006893	0.009730 9	0.478719
Smoking Index	CAD	rs3512097 4	A	G	0.583	-0.012	0.002	2.10E-09	0.001829	0.009386 5	0.845507
Smoking Index	CAD	rs3516960 6	T	G	0.612	0.013	0.002	1.20E-09	0.012571	0.011193	0.26139
Smoking Index	CAD	rs3517583 4	G	A	0.788	-0.024	0.002	4.80E-22	0.011184	0.012028 4	0.352473
Smoking Index	CAD	rs3534334 4	C	A	0.733	0.013	0.002	1.00E-08	0.01511	0.011240 8	0.17888
Smoking Index	CAD	rs3742365	T	C	0.595	-0.016	0.002	2.30E-14	-0.016205	0.009498 4	0.087993 4
Smoking Index	CAD	rs3811038	T	C	0.724	-0.014	0.002	9.20E-10	0.004533	0.010968 1	0.679396
Smoking Index	CAD	rs421983	T	C	0.519	0.013	0.002	3.10E-10	0.00063	0.009154 1	0.945131
Smoking Index	CAD	rs4391802	A	G	0.707	0.015	0.002	1.30E-11	0.004798	0.010221 9	0.638794
Smoking Index	CAD	rs4473348	A	T	0.25	-0.015	0.002	9.00E-11	-0.020153	0.011068 1	0.068634 1
Smoking Index	CAD	rs4671357	T	C	0.519	-0.014	0.002	1.10E-11	-0.008261	0.009452 8	0.382161
Smoking Index	CAD	rs4814873	C	T	0.767	0.014	0.002	2.70E-09	0.021137	0.010907 3	0.052639 3
Smoking Index	CAD	rs4949465	T	C	0.87	-0.017	0.003	1.50E-08	-0.022869	0.012214 1	0.061158 9
Smoking Index	CAD	rs4957528	A	C	0.208	-0.015	0.002	4.50E-09	-0.014558	0.012746 4	0.253401
Smoking Index	CAD	rs549845	G	A	0.301	0.016	0.002	9.90E-14	0.008157	0.009827 6	0.406531

Smoking Index	CAD	rs6011779	C	T	0.191	0.028	0.003	1.60E-27	0.018733	0.013545 9	0.166687
Smoking Index	CAD	rs6095242 8	T	C	0.909	0.019	0.003	3.40E-08	0.014414	0.013881 5	0.299104
Smoking Index	CAD	rs6119897	G	A	0.762	-0.018	0.002	3.10E-15	-0.020157	0.010517 3	0.055295 5
Smoking Index	CAD	rs6209801 3	G	A	0.64	-0.012	0.002	5.60E-09	-0.008057	0.010666 2	0.450021
Smoking Index	CAD	rs6213553 6	C	T	0.968	0.035	0.006	6.80E-10	0.003779	0.029823 8	0.899169
Smoking Index	CAD	rs6215587 4	A	G	0.873	-0.024	0.003	4.00E-16	0.017265	0.015390 4	0.261946
Smoking Index	CAD	rs6217597 2	T	C	0.966	0.031	0.006	1.70E-08	0.030329	0.030435 3	0.319005
Smoking Index	CAD	rs624833	T	G	0.695	0.013	0.002	9.20E-10	0.010431	0.010679 2	0.328689
Smoking Index	CAD	rs6741228	T	C	0.433	0.011	0.002	1.70E-08	0.020156	0.009340 9	0.030942 1
Smoking Index	CAD	rs6759606 7	G	A	0.649	-0.013	0.002	1.10E-09	-0.017072	0.009959	0.086486 8
Smoking Index	CAD	rs6778080	T	C	0.267	0.016	0.002	2.10E-12	0.0106	0.011440 7	0.354177
Smoking Index	CAD	rs6779302	G	T	0.633	-0.013	0.002	1.40E-09	0.002586	0.009791 7	0.791702
Smoking Index	CAD	rs6935954	A	G	0.421	0.014	0.002	9.60E-12	-0.010899	0.009891 6	0.270532
Smoking Index	CAD	rs6957896	C	T	0.503	-0.011	0.002	1.90E-08	-0.00727	0.009551 6	0.446582
Smoking Index	CAD	rs6962772	A	G	0.846	0.016	0.003	8.60E-09	0.008701	0.011447 2	0.447196
Smoking Index	CAD	rs7039819	G	A	0.427	0.013	0.002	5.20E-10	0.014408	0.009486 5	0.128814
Smoking Index	CAD	rs7077678	C	T	0.623	0.012	0.002	2.40E-09	0.011614	0.009335 5	0.213473
Smoking Index	CAD	rs7136754 5	G	A	0.791	-0.015	0.002	1.70E-09	0.003924	0.012202 2	0.74777

Smoking Index	CAD	rs7144406	A	G	0.791	-0.013	0.002	4.20E-08	-0.003584	0.012996 2	0.782723
Smoking Index	CAD	rs7155595	A	C	0.674	-0.013	0.002	3.40E-09	-0.008617	0.010265 3	0.40123
Smoking Index	CAD	rs7267886 4	G	A	0.829	0.018	0.003	1.70E-11	0.010335	0.014001	0.460418
Smoking Index	CAD	rs7297175	T	C	0.431	-0.012	0.002	1.10E-08	0.004107	0.009830 8	0.676117
Smoking Index	CAD	rs732083	G	A	0.333	0.012	0.002	1.40E-08	0.020676	0.009827 6	0.035389 1
Smoking Index	CAD	rs7322054 4	A	C	0.842	-0.016	0.003	1.50E-08	-0.008214	0.013311 3	0.537188
Smoking Index	CAD	rs7333559	G	A	0.212	0.015	0.002	5.30E-10	0.00524	0.012032 7	0.663214
Smoking Index	CAD	rs7408691 1	G	A	0.925	0.021	0.004	2.00E-08	0.001896	0.018969 7	0.920385
Smoking Index	CAD	rs7528604	G	A	0.566	0.014	0.002	6.60E-12	0.010029	0.009310 5	0.281403
Smoking Index	CAD	rs7553348	G	A	0.438	0.014	0.002	5.90E-12	-0.003328	0.00943	0.724151
Smoking Index	CAD	rs7569203	A	C	0.689	-0.016	0.002	5.50E-13	0.000949	0.009842 8	0.92319
Smoking Index	CAD	rs7574240 6	G	A	0.739	0.014	0.002	1.20E-09	0.008049	0.010592 3	0.44732
Smoking Index	CAD	rs7660858 2	C	A	0.953	0.031	0.005	3.40E-10	-0.03298	0.037949 1	0.384815
Smoking Index	CAD	rs7766610	C	A	0.183	0.018	0.003	2.40E-12	0.012158	0.010986 6	0.268458
Smoking Index	CAD	rs7775552	A	G	0.513	-0.012	0.002	2.50E-09	-0.002453	0.009280 1	0.791526
Smoking Index	CAD	rs7807019	A	G	0.54	-0.015	0.002	7.50E-14	-0.018949	0.009187 7	0.039167 9
Smoking Index	CAD	rs8042134	T	G	0.541	-0.014	0.002	2.20E-12	0.013937	0.009704 8	0.150976
Smoking Index	CAD	rs8042849	C	T	0.342	0.028	0.002	2.40E-39	-0.003889	0.010105 6	0.700359
Smoking Index	CAD	rs860326	C	T	0.428	0.012	0.002	3.20E-09	0.007768	0.009569	0.416915



Smoking Index	CAD	rs8614	C	A	0.818	-0.017	0.003	1.50E-10	-0.021264	0.011673 1	0.068512 5
Smoking Index	CAD	rs889398	C	T	0.588	0.013	0.002	3.90E-11	0.026764	0.009708 1	0.005835 53
Smoking Index	CAD	rs912780	T	G	0.65	0.012	0.002	8.50E-09	0.004244	0.009540 8	0.656444
Smoking Index	CAD	rs9435340	T	A	0.344	0.012	0.002	1.00E-08	0.011075	0.009727 6	0.254907
Smoking Index	CAD	rs9842947	C	T	0.326	-0.012	0.002	4.40E-09	-0.000872	0.009900 3	0.929815
Smoking Index	CAD	rs986391	G	A	0.367	0.016	0.002	1.30E-14	-0.000997	0.009545 1	0.916811
Smoking Index	CAD	rs9904288	T	C	0.708	0.012	0.002	2.40E-08	0.045469	0.010333 8	1.07999E- 05
Smoking Index	CAD	rs9919670	G	A	0.612	-0.022	0.002	2.10E-26	0.007256	0.009460 4	0.443089

**eTable 2. Egger Bias Intercept Test for Smoking Index-ASCVD Analysis**

<b>Exposure</b>	<b>Outcome</b>	<b>Egger Intercept</b>	<b>SE</b>	<b>P value</b>
Smoking Index	PAD	-0.0077	0.0052	0.14
Smoking Index	STROKE	-0.0024	0.01	0.81
Smoking Index	CAD	0.01	0.0052	0.046
Smoking Initiation	PAD	-0.002	0.0077	0.79
Smoking Initiation	STROKE	-0.011	0.012	0.35
Smoking Initiation	CAD	-0.0031	0.0068	0.65

The Egger bias intercept test was applied to detect evidence of horizontal pleiotropy in the association between smoking and ASCVD outcomes. The test was applied using both exposures for genetic liability to smoking (lifetime smoking index and smoking initiation). P-values < 0.05 were considered evidence of potential horizontal pleiotropy.

**eTable 3. MR Steiger Directionality Test for Smoking-Cardiometabolic Risk Factor Analysis**

Exposure	Outcome	r <sup>2</sup> exposure	r <sup>2</sup> outcome	Correct causal direction	Steiger pvalue
Smoking Index	Type 2 diabetes	0.01	0.0014	TRUE	3.60E-49
Smoking Index	Chronic kidney disease	0.0089	0.0012	TRUE	4.70E-73
Smoking Index	Overweight	0.0089	0.0012	TRUE	4.60E-90
Smoking Index	Hypertension	0.012	0.0017	TRUE	2.70E-236
Smoking Index	Hyperlipidemia	0.011	0.0016	TRUE	3.40E-224
Smoking Index	eGFR (creatinine)	0.0088	0.001	TRUE	1.70E-88
Smoking Index	Body mass index	0.009	0.0023	TRUE	1.20E-79
Smoking Index	HDL cholesterol	0.0089	0.0013	TRUE	3.00E-63
Smoking Index	LDL cholesterol	0.0089	0.001	TRUE	1.20E-70
Smoking Index	Total cholesterol	0.0089	0.0012	TRUE	1.90E-68
Smoking Index	Triglycerides	0.0089	0.0014	TRUE	4.50E-59
Smoking Index	Waist circumference	0.009	0.0026	TRUE	5.80E-52
Smoking Index	Waist-to-hip ratio	0.009	0.0016	TRUE	2.70E-75
Smoking Index	HbA1C	0.0089	0.0019	TRUE	6.60E-25
Smoking Index	Fasting glucose	0.0091	0.002	TRUE	3.60E-31
Smoking Index	Fasting insulin	0.0091	0.0023	TRUE	3.40E-25
Smoking Index	Interleukin-1 beta	0.012	0.046	FALSE	6.00E-10
Smoking Index	Interleukin-6	0.012	0.035	FALSE	0.0000045
Smoking Index	C-reactive protein	0.012	0.037	FALSE	0.0000014

Smoking Index	Interleukin-6 receptor	0.0097	0.034	FALSE	3.60E-07
Smoking Index	Systolic Blood Pressure	0.012	0.0015	TRUE	3.10E-248

The MR Steiger directionality test was applied to determine the correct direction of effect for the estimated associations between smoking and cardiometabolic risk factors for ASCV.