

ONLINE DATA SUPPLEMENT

Type 2 Diabetes, Glucose, Insulin, BMI and Ischemic Stroke Subtypes: Mendelian Randomization Study

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Table e-1. Single nucleotide polymorphism used as instrumental variables in the Mendelian randomization analyses of type 2 diabetes, fasting glucose, fasting insulin, and body mass index

SNP	Closest gene	Risk factor	Risk factor		All ischemic strokes			Large artery stroke			Small vessel disease			Cardioembolic stroke			Excluded in SA
			EA	Beta	Beta	SE	P-value	Beta	SE	P-value	Beta	SE	P-value	Beta	SE	P-value	
rs10203174	THADA	T2D	C	0.131	-0.0166	0.0257	0.5184	0.0972	0.0512	0.05786	-0.0421	0.046	0.3602	-0.0129	0.0445	0.7725	
rs10278336	GCK	T2D	A	0.068	-0.0004	0.0146	0.9775	0.0084	0.0298	0.7787	0.0021	0.0299	0.9449	0.0022	0.0265	0.9349	Yes*
rs10401969	CILP2	T2D	C	0.122	-0.0112	0.0276	0.6845	0.0155	0.0555	0.7798	0.0955	0.0543	0.07834	-0.0504	0.0511	0.3243	Yes†
rs10811661	CDKN2A/B	T2D	T	0.166	0.0041	0.0194	0.8339	-0.0178	0.0391	0.6482	0.0503	0.0399	0.2082	-0.0226	0.0347	0.5162	Yes*
rs10830963	MTNR1B	T2D	G	0.095	-0.0109	0.0172	0.5275	0.0874	0.0354	0.01362	-0.0149	0.0353	0.6739	-0.0102	0.0313	0.745	Yes*
rs10842994	KLHDC5	T2D	C	0.095	0.0104	0.0183	0.5698	0.026	0.0382	0.4952	-0.0515	0.0373	0.1669	0.0503	0.0339	0.1373	
rs10923931	NOTCH2	T2D	T	0.077	0.037	0.0234	0.1148	0.121	0.0475	0.01086	-0.0087	0.0486	0.8585	0.0689	0.0424	0.1041	
rs11063069	CCND2	T2D	G	0.077	-0.0002	0.0196	0.9935	0.0087	0.0411	0.8327	0.0539	0.0398	0.1758	-0.0065	0.0357	0.8565	
rs1111875	HHEX/IDE	T2D	C	0.104	-0.0278	0.0146	0.05692	0.0006	0.0298	0.9847	-0.024	0.0301	0.4259	-0.0348	0.0265	0.1892	
rs11257655	CDC123/CAMK1D	T2D	T	0.068	-0.0007	0.0182	0.968	-0.0479	0.0388	0.2173	0.0248	0.0378	0.5109	-0.0162	0.033	0.6237	
rs11634397	ZFAND6	T2D	G	0.049	0.0223	0.0153	0.1452	0.0006	0.0309	0.9851	-0.0022	0.031	0.9436	0.0227	0.0278	0.4147	
rs11717195	ADCY5	T2D	T	0.104	0.0222	0.0173	0.1978	0.0238	0.0353	0.4999	0.0152	0.0355	0.6683	0.0521	0.0319	0.1025	Yes*
rs12427353	HNF1A (TCF1)	T2D	G	0.077	-0.0001	0.0184	0.9971	0.0044	0.0378	0.9081	0.007	0.0378	0.8536	0.0035	0.0335	0.9158	
rs12571751	ZMIZ1	T2D	A	0.077	0.0119	0.0144	0.4083	0.0288	0.0295	0.3282	0.0505	0.0297	0.08915	-0.0204	0.0261	0.4359	
rs12899811	PRC1	T2D	G	0.077	0.0008	0.0157	0.9599	0.0262	0.0313	0.4016	0.0368	0.0315	0.243	0.0216	0.0279	0.4395	
rs12970134	MC4R	T2D	A	0.077	0.019	0.0168	0.2567	-0.0016	0.0356	0.9636	-0.0095	0.0356	0.7891	0.0727	0.0303	0.01662	Yes*
rs13233731	KLF14	T2D	G	0.049	0.0012	0.0143	0.9335	-0.0018	0.029	0.9493	0.0344	0.0293	0.2411	0.018	0.0259	0.4867	Yes†
rs13389219	GRB14	T2D	C	0.068	0.0001	0.0147	0.9922	0.0393	0.03	0.1901	0.0277	0.0302	0.3581	-0.0136	0.0266	0.6087	Yes*†
rs1359790	SPRY2	T2D	G	0.077	0.0214	0.0162	0.1868	0.0036	0.033	0.9132	-0.03	0.033	0.3636	0.0335	0.0295	0.2565	
rs1496653	UBE2E2	T2D	A	0.086	0.0031	0.018	0.8618	-0.0247	0.036	0.4935	0.0124	0.0369	0.7373	-0.0197	0.0326	0.5456	
rs1552224	ARAP1 (CENTD2)	T2D	A	0.104	0.0131	0.0219	0.5496	-0.002	0.0451	0.9638	-0.0456	0.0452	0.3136	0.0094	0.0395	0.8124	Yes*
rs163184	KCNQ1	T2D	G	0.086	0.0273	0.0145	0.05955	0.0219	0.0299	0.4652	0.0309	0.0297	0.2985	0.026	0.0265	0.3269	
rs17168486	DGKB	T2D	T	0.104	-0.002	0.0191	0.9155	-0.0101	0.0392	0.797	0.0157	0.0394	0.6908	0.0287	0.0347	0.4075	Yes*
rs17791513	TLE4	T2D	A	0.113	0.0465	0.0308	0.1314	0.0765	0.0654	0.242	0.0587	0.0637	0.3562	-0.0417	0.0547	0.4454	
rs1801282	PPARG	T2D	C	0.122	0.0249	0.0216	0.2496	-0.047	0.0432	0.2765	0.0077	0.0448	0.8632	0.0426	0.0394	0.2793	Yes*
rs2075423	PROX1	T2D	G	0.068	0.0064	0.0151	0.6706	-0.0046	0.0308	0.8803	0.0023	0.0311	0.942	-0.0308	0.0275	0.2622	Yes*
rs2261181	HMGGA2	T2D	T	0.122	-0.006	0.0236	0.7995	0.0605	0.0474	0.2017	0.064	0.0474	0.177	-0.0422	0.043	0.3266	
rs2334499	HCCA2	T2D	T	0.039	0.0068	0.015	0.651	0.0695	0.0313	0.02638	0.0344	0.0307	0.2617	-0.0202	0.0278	0.4672	

rs243088	<i>BCL11A</i>	T2D	T	0.068	0.0096	0.0144	0.5051	0.0179	0.0292	0.54	0.0173	0.0296	0.5592	0.0217	0.0261	0.405	
rs2796441	<i>TLE1</i>	T2D	G	0.068	0.0057	0.015	0.7044	-0.0011	0.0308	0.9704	0.0211	0.0308	0.4935	-0.0117	0.0274	0.6695	
rs2943640	<i>IRS1</i>	T2D	C	0.095	0.0083	0.015	0.5783	0.0341	0.0309	0.2697	0.0561	0.0311	0.0711	-0.0185	0.0272	0.4956	Yes*†
rs3802177	<i>SLC30A8</i>	T2D	G	0.131	0.0273	0.0156	0.08044	0.0696	0.032	0.02967	0.0143	0.032	0.6539	0.0115	0.0282	0.683	Yes*
rs4402960	<i>IGF2BP2</i>	T2D	T	0.122	0.0238	0.0154	0.1216	0.0437	0.0314	0.1639	0.0542	0.0315	0.08562	0.0259	0.0279	0.3532	Yes*
rs4430796	<i>HNF1B (TCF2)</i>	T2D	G	0.122	-0.0033	0.0144	0.8191	0.0194	0.0292	0.5068	0.0002	0.0295	0.9953	-0.0138	0.0261	0.598	
rs4458523	<i>WFS1</i>	T2D	G	0.095	0.0022	0.0146	0.8799	0.0006	0.0299	0.9846	0.0053	0.03	0.861	0.0325	0.0267	0.2234	
rs459193	<i>ANKRD55</i>	T2D	G	0.077	-0.0085	0.0166	0.6105	0.0037	0.0338	0.9131	-0.0194	0.0342	0.5709	-0.0092	0.0301	0.7591	Yes*†
rs516946	<i>ANK1</i>	T2D	C	0.086	0.0019	0.0168	0.9095	-0.0256	0.0338	0.4485	0.073	0.0347	0.03536	-0.0303	0.0302	0.3155	
rs5215	<i>KCNJ11</i>	T2D	C	0.068	0.0576	0.0149	0.0001067	0.0204	0.0303	0.5011	0.0872	0.0303	0.00395	0.0796	0.0268	0.003012	
rs6795735	<i>ADAMTS9</i>	T2D	C	0.077	0.0469	0.0146	0.001325	0.0823	0.0297	0.005632	0.0358	0.0299	0.2316	0.0468	0.0264	0.07636	
rs6878122	<i>ZBED3</i>	T2D	G	0.095	0.0446	0.0157	0.004615	0.0295	0.0321	0.3589	0.0757	0.0321	0.01816	0.0035	0.0289	0.9036	Yes*
rs7177055	<i>HMG20A</i>	T2D	A	0.077	0.0125	0.0158	0.4302	0.0295	0.0319	0.3546	-0.0136	0.0323	0.6724	0.0182	0.0284	0.5211	
rs7202877	<i>BCAR1</i>	T2D	T	0.113	0.0098	0.0241	0.6859	-0.0127	0.0492	0.7962	-0.069	0.0483	0.1532	-0.0131	0.0436	0.7633	
rs7756992	<i>CDKAL1</i>	T2D	G	0.157	0.0044	0.0159	0.7819	0.0194	0.0323	0.5478	0.022	0.0326	0.4988	-0.0085	0.029	0.768	Yes*
rs780094	<i>GCKR</i>	T2D	C	0.058	-0.006	0.0166	0.7172	-0.0323	0.0322	0.3156	-0.0075	0.0299	0.8018	0.0003	0.0288	0.9919	Yes*†
rs7845219	<i>TP53INP1</i>	T2D	T	0.058	0.002	0.0143	0.8881	0.0222	0.0292	0.4464	0.025	0.0295	0.3959	-0.0183	0.026	0.4823	
rs7903146	<i>TCF7L2</i>	T2D	T	0.329	0.0427	0.018	0.01736	0.1069	0.0346	0.001981	0.0621	0.0374	0.09669	0.0323	0.0313	0.3022	Yes*
rs7955901	<i>TSPAN8/LGR5</i>	T2D	C	0.068	0.0218	0.0143	0.1278	0.122	0.0292	0.0000292	0.0208	0.0294	0.478	-0.0021	0.0261	0.9358	
rs8108269	<i>GIPR</i>	T2D	G	0.068	0.0133	0.0157	0.3974	0.0312	0.0324	0.3359	-0.0202	0.0324	0.5327	0.0101	0.0286	0.7233	Yes*†
rs849135	<i>JAZF1</i>	T2D	G	0.104	0.0095	0.0144	0.5116	-0.0005	0.0292	0.9851	0.0379	0.0294	0.1973	-0.0189	0.0261	0.4685	
rs10747083	<i>P2RX2</i>	Glucose	A	0.013	0.0255	0.0166	0.124	0.0038	0.0332	0.9079	0.0451	0.0331	0.172	-0.0133	0.0298	0.6555	
rs10811661	<i>CDKN2B</i>	Glucose	T	0.024	0.0041	0.0194	0.8339	-0.0178	0.0391	0.6482	0.0503	0.0399	0.2082	-0.0226	0.0347	0.5162	Yes*
rs10830963	<i>MTNR1B</i>	Glucose	G	0.078	-0.0109	0.0172	0.5275	0.0874	0.0354	0.01362	-0.0149	0.0353	0.6739	-0.0102	0.0313	0.745	Yes*
rs10885122	<i>ADRA2A</i>	Glucose	G	0.027	0.0187	0.0219	0.3919	-0.051	0.0436	0.2418	0.0192	0.0453	0.6718	0.0101	0.0394	0.7984	
rs11071657	<i>VPS13C/C2CD4A/B</i>	Glucose	A	0.010	-0.0232	0.015	0.1213	-0.0613	0.0305	0.04444	-0.0232	0.0306	0.4483	-0.0216	0.0274	0.4305	
rs11558471	<i>SLC30A8</i>	Glucose	A	0.029	0.0258	0.0156	0.09795	0.0711	0.0319	0.02601	0.0122	0.0319	0.7022	0.0099	0.0281	0.7253	Yes*
rs11603334	<i>ARAP1</i>	Glucose	G	0.019	0.0127	0.0219	0.5609	-0.0022	0.0451	0.9619	-0.0475	0.0452	0.2931	0.0094	0.0395	0.8124	Yes*
rs11605924	<i>CRY2</i>	Glucose	A	0.020	-0.0118	0.0144	0.4122	-0.0272	0.0294	0.3542	-0.025	0.0294	0.396	0.0153	0.0262	0.5608	
rs11619319	<i>PDX1</i>	Glucose	G	0.019	0.0017	0.0171	0.9202	0.0317	0.0346	0.3588	0.0268	0.0348	0.4402	-0.0391	0.0313	0.212	
rs11708067	<i>ADCY5</i>	Glucose	A	0.023	0.0293	0.0174	0.09226	0.0378	0.0356	0.2878	0.0174	0.0357	0.626	0.0585	0.0321	0.06831	Yes*
rs11715915	<i>AMT</i>	Glucose	C	0.012	0.0247	0.0181	0.1705	0.0143	0.0353	0.6852	0.0545	0.0382	0.1536	0.0391	0.0315	0.2149	
rs11920090	<i>SLC2A2</i>	Glucose	T	0.026	-0.0006	0.021	0.9763	0.0341	0.0428	0.4251	-0.0093	0.0431	0.8283	-0.0582	0.0374	0.12	

rs16913693	<i>IKBKAP</i>	Glucose	T	0.043	-0.0222	0.0457	0.6266	-0.0015	0.0966	0.9875	-0.0075	0.0995	0.9399	-0.0804	0.0825	0.3295	
rs174550	<i>FADS1</i>	Glucose	T	0.019	0.0226	0.0153	0.1394	0.0856	0.0315	0.006654	-0.0504	0.0314	0.1082	0.0453	0.028	0.1055	Yes†
rs17762454	<i>RREB1</i>	Glucose	T	0.014†	-0.0022	0.0163	0.8942	-0.0203	0.0335	0.5453	-0.0048	0.0336	0.8873	0.011	0.0295	0.7086	
rs2191349	<i>DGKB/TMEM195</i>	Glucose	T	0.029	0.0118	0.0144	0.4161	0.0411	0.0296	0.1653	-0.0175	0.0297	0.5562	0.0251	0.0264	0.3403	Yes*
rs2302593	<i>GIPR</i>	Glucose	C	0.014	-0.0099	0.0146	0.5001	0.0132	0.0301	0.6623	-0.0398	0.0299	0.1831	-0.0068	0.0268	0.7981	Yes†
rs2657879	<i>GLS2</i>	Glucose	G	0.016†	-0.0019	0.0186	0.9193	-0.0038	0.0377	0.919	0.016	0.0381	0.675	-0.0421	0.0339	0.2143	
rs340874	<i>PROX1</i>	Glucose	C	0.013	-0.0136	0.0144	0.3465	-0.0274	0.0293	0.3505	-0.0039	0.0296	0.8946	-0.0262	0.0262	0.3178	Yes*
rs3783347	<i>WARS</i>	Glucose	G	0.017	0.0445	0.0177	0.01189	0.0398	0.0359	0.268	0.0528	0.0366	0.1488	-0.0086	0.0319	0.7884	
rs3829109	<i>LOC728489</i>	Glucose	G	0.017	0.046	0.0174	0.008364	0.0704	0.0349	0.04369	0.0607	0.0358	0.08986	0.0809	0.0316	0.01053	
rs4506565	<i>TCF7L2</i>	Glucose	T	0.021	0.0445	0.0176	0.01145	0.0917	0.0339	0.006898	0.0828	0.0366	0.02351	0.0179	0.0306	0.5595	Yes*
rs4607517	<i>GCK</i>	Glucose	A	0.057	0.0063	0.0194	0.7445	0.0342	0.038	0.3683	0.0154	0.0388	0.691	-0.0358	0.0349	0.3053	Yes*
rs4869272	<i>PCSK1</i>	Glucose	T	0.018	-0.001	0.0154	0.947	0.0088	0.0313	0.7789	-0.0327	0.0318	0.3038	0.0347	0.0282	0.2193	
rs560887	<i>G6PC2</i>	Glucose	C	0.071	-0.0192	0.0156	0.2209	-0.0403	0.0317	0.2031	-0.0415	0.032	0.1948	-0.0176	0.0285	0.5369	
rs576674	<i>KL</i>	Glucose	G	0.017	0.0469	0.0189	0.01305	-0.0018	0.0386	0.9618	0.088	0.0383	0.02148	0.0327	0.0342	0.3396	
rs6072275	<i>TOP1</i>	Glucose	A	0.016	0.0151	0.02	0.4497	0.1063	0.0403	0.00844	-0.0105	0.0412	0.799	0.0175	0.0363	0.6289	
rs6113722	<i>FOXA2</i>	Glucose	G	0.035	-0.0199	0.037	0.5897	-0.0388	0.0761	0.6101	0.132	0.08	0.09872	-0.0783	0.0652	0.2303	
rs6943153	<i>GRB10</i>	Glucose	T	0.015	-0.0091	0.0156	0.5587	0.0046	0.0318	0.8841	-0.0436	0.0319	0.1719	-0.04	0.0285	0.161	
rs7651090	<i>IGF2BP2</i>	Glucose	G	0.013	0.0256	0.0154	0.09565	0.0465	0.0313	0.1374	0.0665	0.0315	0.03507	0.028	0.0279	0.3157	Yes*
rs7708285	<i>ZBED3</i>	Glucose	G	0.015†	0.0417	0.0159	0.008766	0.0422	0.0325	0.1936	0.0678	0.0324	0.03615	-0.0047	0.0292	0.8723	Yes*
rs780094	<i>GCKR</i>	Glucose	C	0.027	-0.006	0.0166	0.7172	-0.0323	0.0322	0.3156	-0.0075	0.0299	0.8018	0.0003	0.0288	0.9919	Yes*†
rs7867224	<i>GLIS3</i>	Glucose	A	0.013	0.0172	0.0143	0.2301	0.0273	0.0291	0.348	0.0566	0.0295	0.05489	0.0076	0.026	0.7694	
rs7944584	<i>MADD</i>	Glucose	A	0.023	-0.0052	0.016	0.7458	-0.0572	0.0323	0.07656	0.0254	0.033	0.442	0.0367	0.0291	0.2078	
rs9368222	<i>CDKAL1</i>	Glucose	A	0.014	0.0034	0.016	0.8323	0.0161	0.0324	0.6208	0.0181	0.0329	0.5823	-0.013	0.0292	0.6572	Yes*
rs983309	<i>PPP1R3B</i>	Glucose	T	0.026	0.0269	0.0231	0.2431	0.001	0.0474	0.9839	0.0103	0.0481	0.8299	0.0595	0.042	0.1568	Yes*†
rs10195252	<i>GRB14</i>	Insulin	T	0.016	-0.0048	0.0146	0.7415	0.034	0.0298	0.254	0.024	0.0299	0.4214	-0.0208	0.0264	0.4317	Yes*†
rs1167800	<i>HIP1</i>	Insulin	A	0.016	0.037	0.0147	0.01215	0.0623	0.0305	0.04098	0.0484	0.0303	0.1106	-0.0251	0.0269	0.352	Yes*
rs1530559	<i>YSK4</i>	Insulin	A	0.015	-0.0046	0.0165	0.7808	-0.0217	0.0335	0.5172	-0.0226	0.0337	0.5014	-0.0224	0.0296	0.4495	
rs17036328	<i>PPARG</i>	Insulin	T	0.021†	0.0193	0.0215	0.368	-0.0398	0.0428	0.3519	-0.0074	0.0446	0.8687	0.0527	0.0391	0.1776	Yes*
rs2126259	<i>PPP1R3B</i>	Insulin	T	0.024†	0.015	0.0245	0.5404	0.0246	0.0496	0.6195	-0.0051	0.051	0.9198	0.047	0.0446	0.2921	Yes*
rs2745353	<i>RSPO3</i>	Insulin	T	0.014	0.0091	0.0143	0.5216	0.0266	0.029	0.3599	-0.0289	0.0292	0.3219	0.0163	0.0259	0.5275	Yes†
rs2943645	<i>IRS1</i>	Insulin	T	0.019	0.0031	0.0149	0.8374	0.0333	0.0306	0.2764	0.0097	0.0308	0.7522	-0.0103	0.027	0.7041	Yes*†
rs3822072	<i>FAM13A1</i>	Insulin	A	0.012†	0.0337	0.0146	0.02066	0.093	0.0297	0.00176	0.0266	0.0298	0.3735	0.0231	0.0264	0.3829	Yes†
rs459193	<i>ANKRD55-MAP3KI</i>	Insulin	G	0.015†	-0.0085	0.0166	0.6105	0.0037	0.0338	0.9131	-0.0194	0.0342	0.5709	-0.0092	0.0301	0.7591	Yes*†

rs4846565	<i>LYPLAL1</i>	Insulin	G	0.013#	-0.0268	0.0153	0.07993	-0.014	0.0311	0.6533	-0.034	0.0313	0.2768	-0.0283	0.0278	0.3077	
rs4865796	<i>ARL15</i>	Insulin	A	0.015	0.01	0.0156	0.5232	0.0347	0.0322	0.2813	0.0442	0.0322	0.17	-0.03	0.0284	0.2916	
rs6822892	<i>PDGFC</i>	Insulin	A	0.014#	0.0168	0.0153	0.272	0.0143	0.0328	0.6623	0.005	0.0311	0.8721	0.0183	0.0277	0.5088	
rs6912327	<i>C6orf107</i>	Insulin	T	0.017	-0.0381	0.0171	0.02551	-0.1032	0.0343	0.002658	0.0328	0.0351	0.3492	0.0175	0.031	0.572	
rs731839	<i>PEPD</i>	Insulin	G	0.015	0.0256	0.0153	0.094	0.0829	0.0307	0.00697	0.0519	0.0313	0.09716	0.0354	0.0276	0.2003	Yes†
rs780094	<i>GCKR</i>	Insulin	C	0.019	-0.006	0.0166	0.7172	-0.0323	0.0322	0.3156	-0.0075	0.0299	0.8018	0.0003	0.0288	0.9919	Yes†
rs7903146	<i>TCF7L2</i>	Insulin	C	0.018	-0.0427	0.018	0.01736	-0.1069	0.0346	0.001981	-0.0621	0.0374	0.09669	-0.0323	0.0313	0.3022	Yes*
rs860598	<i>IGF1</i>	Insulin	A	0.018	-0.0064	0.0191	0.7364	0.0729	0.0398	0.06681	0.0355	0.0395	0.3688	-0.0995	0.0343	0.003754	Yes*
rs974801	<i>TET2</i>	Insulin	G	0.014#	-0.0219	0.0148	0.1408	-0.0036	0.03	0.9036	-0.0444	0.0305	0.1451	-0.0025	0.0268	0.9258	
rs1000940	<i>RABEP1</i>	BMI	G	0.019	-0.0098	0.0155	0.53	-0.0004	0.0315	0.9905	-0.0224	0.0319	0.4823	0.0201	0.0281	0.4746	
rs10132280	<i>STXBP6</i>	BMI	C	0.023	0.0099	0.0157	0.5283	0.0513	0.0322	0.111	-0.0397	0.032	0.2142	0.027	0.0284	0.3413	
rs1016287	<i>LINC01122</i>	BMI	T	0.023	0.0116	0.0158	0.4598	-0.0205	0.0322	0.524	0.0016	0.0324	0.9596	0.0254	0.0286	0.3755	
rs10182181	<i>ADCY3</i>	BMI	G	0.031	-0.0063	0.0163	0.6967	-0.0268	0.0314	0.3937	-0.0268	0.0294	0.3615	-0.0833	0.0283	0.003211	
rs10733682	<i>LMX1B</i>	BMI	A	0.017	-0.0164	0.0143	0.2507	0.003	0.0289	0.9177	-0.0164	0.0293	0.5765	-0.0185	0.0259	0.4757	
rs10938397	<i>GNPDA2</i>	BMI	G	0.040	0.0121	0.0146	0.4072	0.0382	0.0302	0.2057	0.0627	0.03	0.03648	-0.0131	0.0268	0.6245	
rs10968576	<i>LINGO2</i>	BMI	G	0.025	-0.0077	0.0155	0.6184	-0.0265	0.0316	0.4021	0.0135	0.032	0.672	-0.0036	0.0282	0.8987	
rs11030104	<i>BDNF</i>	BMI	A	0.041	0.0392	0.018	0.0291	0.0442	0.0377	0.2402	0.0415	0.038	0.2753	0.0405	0.0324	0.2115	Yes§
rs11057405	<i>CLIP1</i>	BMI	G	0.031	-0.078	0.0246	0.001504	-0.0871	0.0498	0.0805	-0.1698	0.0501	0.000702	-0.0807	0.0445	0.06991	
rs11126666	<i>KCNK3</i>	BMI	A	0.021	0.0322	0.0184	0.07986	0.0861	0.0351	0.01415	-0.0054	0.0336	0.8725	0.0223	0.0319	0.4848	
rs11165643	<i>PTBP2</i>	BMI	T	0.022	-0.0197	0.0147	0.1803	-0.0655	0.0295	0.02667	0.0026	0.0302	0.9318	0.0119	0.0264	0.6529	
rs11191560	<i>NT5C2</i>	BMI	C	0.031	-0.011	0.0249	0.6573	-0.1477	0.0522	0.004677	-0.0195	0.0509	0.7011	0.0212	0.0442	0.6314	
rs11583200	<i>ELAVL4</i>	BMI	C	0.018	0.0051	0.0147	0.7271	0.0758	0.0296	0.01051	-0.023	0.0304	0.4497	-0.0028	0.0267	0.9176	
rs1167827	<i>HIP1</i>	BMI	G	0.02	0.0248	0.0147	0.09193	0.0289	0.0298	0.3316	0.0582	0.0303	0.05518	-0.0692	0.0265	0.008975	Yes*
rs11688816	<i>EHBP1</i>	BMI	G	0.017	0.0149	0.0143	0.2976	0.0136	0.0296	0.646	0.0224	0.0294	0.4457	0.0386	0.0261	0.1382	
rs11727676	<i>HHIP</i>	BMI	T	0.036	-0.0219	0.027	0.4176	-0.1187	0.058	0.04062	-0.0215	0.0543	0.6921	-0.0272	0.0491	0.5793	
rs11847697	<i>PRKD1</i>	BMI	T	0.049	0.0468	0.0354	0.1865	0.0682	0.0731	0.3505	0.1964	0.0683	0.004017	0.0189	0.0654	0.7722	
rs12016871	<i>MTIF3</i>	BMI	T	0.030	0.1162	0.1087	0.2851	-0.0185	0.3345	0.9559	0.1811	0.1975	0.3592	-0.3912	0.3266	0.231	
rs12286929	<i>CADM1</i>	BMI	G	0.022	0.0083	0.0143	0.5637	0.0122	0.0292	0.6751	0.0667	0.0296	0.02403	0.0008	0.0261	0.9764	
rs12401738	<i>FUBP1</i>	BMI	A	0.021	0.0204	0.0151	0.175	0.0316	0.0307	0.3037	0.0517	0.031	0.09509	0.0056	0.0275	0.8381	
rs12429545	<i>OLFM4</i>	BMI	A	0.033	0.0396	0.0215	0.06499	0.0513	0.0434	0.2375	0.0594	0.0439	0.1762	0.0391	0.0388	0.3129	
rs12446632	<i>GPRC5B</i>	BMI	G	0.040	-0.0136	0.0203	0.5022	-0.0404	0.0404	0.3173	0.0036	0.0414	0.9312	0.0244	0.0368	0.5069	
rs12566985	<i>FPGT-TNNI3K</i>	BMI	G	0.024	-0.0026	0.0144	0.8545	-0.0263	0.0293	0.3693	-0.0218	0.0297	0.4632	-0.0416	0.0263	0.1131	
rs12885454	<i>PRKD1</i>	BMI	C	0.021	0.019	0.0151	0.2088	-0.0101	0.0306	0.7425	0.0268	0.031	0.3875	0.0297	0.0275	0.2799	

rs12940622	<i>RPTOR</i>	BMI	G	0.018	0.0002	0.0144	0.9874	0.0213	0.0292	0.4652	-0.0014	0.0293	0.9625	-0.0273	0.0259	0.2928	
rs13021737	<i>TMEM18</i>	BMI	G	0.060	0.0065	0.0191	0.734	0.0606	0.0395	0.1247	-0.0013	0.0392	0.9737	-0.0271	0.0345	0.4313	
rs13078960	<i>CADM2</i>	BMI	G	0.030	-0.0115	0.0179	0.5216	0.0359	0.0362	0.3214	-0.0167	0.0368	0.6505	-0.0097	0.0324	0.7639	
rs13107325	<i>SLC39A8</i>	BMI	T	0.048	0.0134	0.0271	0.6211	0.0465	0.0549	0.3964	0.0208	0.0556	0.7092	-0.0078	0.0497	0.8746	Yes†
rs13191362	<i>PARK2</i>	BMI	A	0.028	-0.033	0.0224	0.1402	-0.0076	0.0466	0.8706	0.0229	0.0465	0.6228	-0.0761	0.0404	0.05966	
rs1516725	<i>ETV5</i>	BMI	C	0.045	-0.0027	0.0211	0.8992	-0.002	0.0434	0.9629	-0.0312	0.0431	0.4692	0.0541	0.0391	0.1666	
rs1528435	<i>UBE2E3</i>	BMI	T	0.018	-0.0126	0.0148	0.3964	0.0039	0.0301	0.896	-0.0238	0.0304	0.4329	-0.0609	0.0267	0.02243	
rs1558902	<i>FTO</i>	BMI	A	0.082	-0.0004	0.0146	0.9775	0.0283	0.0296	0.3391	-0.0095	0.0298	0.7505	0.0051	0.0263	0.8455	Yes†
rs16851483	<i>RASA2</i>	BMI	T	0.048	0.0389	0.0284	0.1712	0.0037	0.0586	0.95	0.0835	0.0572	0.1441	0.1017	0.0509	0.04584	
rs16951275	<i>MAP2K5</i>	BMI	T	0.031	0.023	0.0173	0.1821	-0.0297	0.0349	0.3951	0.1095	0.0362	0.002503	0.0177	0.0316	0.5747	
rs17001654	<i>SCARB2</i>	BMI	G	0.031	-0.0218	0.0201	0.2787	-0.0289	0.0412	0.484	0.0099	0.041	0.8098	-0.0058	0.0364	0.8724	
rs17024393	<i>GNAT2</i>	BMI	C	0.066	0.0395	0.0431	0.3593	0.0613	0.0871	0.4818	0.1168	0.0894	0.1912	-0.0022	0.0766	0.9775	
rs17094222	<i>HIF1AN</i>	BMI	C	0.025	0.0095	0.0178	0.5928	-0.0293	0.0362	0.4184	-0.0029	0.0367	0.9376	0.0262	0.0322	0.4164	
rs17405819	<i>HNFB4G</i>	BMI	T	0.022	-0.007	0.0157	0.6549	-0.0311	0.0316	0.3248	-0.0173	0.032	0.5878	-0.027	0.0281	0.3366	
rs17724992	<i>PGPEP1</i>	BMI	A	0.019	0.0369	0.0164	0.02423	0.0783	0.0335	0.01938	0.0544	0.0336	0.1056	0.0375	0.0297	0.2072	
rs1808579	<i>C18orf8</i>	BMI	C	0.017	0.0116	0.0144	0.4189	0.0308	0.0292	0.291	-0.018	0.0294	0.5405	0.0343	0.0261	0.1883	
rs1928295	<i>TLR4</i>	BMI	T	0.019	-0.0175	0.0144	0.2258	-0.0075	0.0295	0.7979	-0.0424	0.0296	0.1528	0.0237	0.0262	0.3667	
rs2033529	<i>TDRG1</i>	BMI	G	0.019	-0.012	0.0158	0.4466	0.0238	0.0319	0.4562	-0.0241	0.0325	0.4572	-0.002	0.0286	0.9442	
rs2033732	<i>RALYL</i>	BMI	C	0.019	-0.0023	0.0168	0.8908	-0.0272	0.034	0.4234	-0.0307	0.0342	0.3687	0.0659	0.031	0.03338	
rs205262	<i>C6orf106</i>	BMI	G	0.022	0.0315	0.0159	0.04732	0.0859	0.0322	0.007584	-0.002	0.0326	0.9517	0.0228	0.0289	0.4288	Yes†
rs2075650	<i>TOMM40</i>	BMI	A	0.026	0.0089	0.0208	0.6673	-0.0469	0.0417	0.2607	0.0082	0.0436	0.8514	0.0107	0.038	0.7784	Yes†
rs2112347	<i>POC5</i>	BMI	T	0.026	0.0007	0.0162	0.967	0.0114	0.0325	0.7255	-0.056	0.0334	0.09321	-0.0005	0.0294	0.9856	Yes†
rs2121279	<i>LRP1B</i>	BMI	T	0.025	-0.018	0.0217	0.4052	-0.0381	0.0444	0.3908	-0.0123	0.0452	0.7865	-0.0095	0.039	0.8075	
rs2176598	<i>HSD17B12</i>	BMI	T	0.020	0.0541	0.0166	0.001141	0.0639	0.034	0.05981	0.0892	0.0339	0.008447	0.0478	0.0302	0.1135	
rs2207139	<i>TFAP2B</i>	BMI	G	0.045	0.0346	0.0189	0.06698	0.0405	0.0379	0.2856	0.0205	0.0387	0.5973	0.0161	0.0341	0.6377	
rs2245368	<i>PMS2L11</i>	BMI	C	0.032	-0.0245	0.0253	0.3324	-0.0147	0.0531	0.7815	-0.0679	0.0513	0.186	-0.0045	0.0436	0.9173	
rs2287019	<i>QPCTL</i>	BMI	C	0.036	-0.0052	0.0184	0.7794	0.0249	0.0383	0.5151	-0.0414	0.0374	0.268	0.0064	0.0338	0.8498	Yes†
rs2365389	<i>FHIT</i>	BMI	C	0.020	0.0091	0.0146	0.533	0.0104	0.0297	0.7264	0.0023	0.03	0.9387	0.0045	0.0265	0.8647	
rs2650492	<i>SBK1</i>	BMI	A	0.021	0.0081	0.0162	0.6167	0.0386	0.032	0.2283	-0.0165	0.0328	0.6161	0.0012	0.0289	0.9658	
rs2820292	<i>NAV1</i>	BMI	C	0.020	0.0068	0.0144	0.6396	0.0108	0.0293	0.7116	0.0055	0.0296	0.8523	0.0056	0.026	0.8287	
rs29941	<i>KCTD15</i>	BMI	G	0.018	0.0182	0.0156	0.2428	0.0562	0.0329	0.08803	0.0124	0.0322	0.6999	0.0267	0.0289	0.3562	
rs3101336	<i>NEGR1</i>	BMI	C	0.033	-0.011	0.0147	0.4543	-0.0238	0.0299	0.4261	-0.0701	0.0302	0.02	0	0.0268	0.9995	
rs3736485	<i>DMXL2</i>	BMI	A	0.018	-0.0055	0.0145	0.7064	-0.026	0.0295	0.3779	0.0171	0.0297	0.564	0.0406	0.0262	0.1221	

rs3810291	<i>ZC3H4</i>	BMI	A	0.028	0.0077	0.0164	0.6405	0.0196	0.0346	0.5705	-0.0104	0.0336	0.7582	-0.0039	0.0303	0.8972	
rs3817334	<i>MTCH2</i>	BMI	T	0.026	0.0064	0.0146	0.6629	0.0111	0.0296	0.7076	0.0466	0.0297	0.1166	-0.0007	0.0264	0.978	
rs3849570	<i>GBE1</i>	BMI	A	0.019	0.0193	0.0154	0.2098	0.0459	0.0311	0.1392	0.0465	0.0315	0.1393	-0.0045	0.0278	0.8708	
rs3888190	<i>ATP2A1</i>	BMI	A	0.031	0.0072	0.0147	0.6256	0.0229	0.0299	0.4429	-0.011	0.0302	0.7149	0.0298	0.0266	0.2628	
rs4256980	<i>TRIM66</i>	BMI	G	0.021	-0.0171	0.0149	0.2528	0.0503	0.0305	0.09932	-0.0375	0.0306	0.2208	-0.0319	0.027	0.2373	
rs4740619	<i>C9orf93</i>	BMI	T	0.018	0.011	0.0144	0.4457	0.0151	0.0295	0.6096	-0.0103	0.0296	0.7281	-0.0123	0.0263	0.6396	
rs543874	<i>SEC16B</i>	BMI	G	0.048	-0.0087	0.0183	0.634	0.0145	0.037	0.6948	-0.0394	0.0378	0.2969	0.0141	0.0332	0.6706	
rs6477694	<i>EPB41L4B</i>	BMI	C	0.017	0.0242	0.015	0.1076	0.0726	0.0303	0.01666	-0.0041	0.0309	0.8933	0.0645	0.0272	0.01751	
rs6567160	<i>MC4R</i>	BMI	C	0.056	-0.0075	0.017	0.6592	-0.0223	0.0349	0.5221	-0.0408	0.0356	0.252	0.0274	0.0308	0.3728	Yes†
rs657452	<i>AGBL4</i>	BMI	A	0.023	0.0145	0.0148	0.3263	0.0472	0.0297	0.1123	-0.0199	0.0304	0.5142	0.0241	0.0267	0.3672	
rs6804842	<i>RARB</i>	BMI	G	0.019	-0.0108	0.0144	0.4543	-0.0399	0.0293	0.1725	-0.047	0.0297	0.1132	-0.0121	0.0262	0.6447	
rs7138803	<i>BCDIN3D</i>	BMI	A	0.032	0.0228	0.0148	0.1223	-0.0085	0.0301	0.7766	0.0355	0.0303	0.2401	0.0638	0.0267	0.017	
rs7141420	<i>NRXN3</i>	BMI	T	0.024	0.0324	0.0143	0.02339	-0.0073	0.029	0.8023	0.0362	0.0294	0.2184	0.0558	0.0259	0.03099	
rs7243357	<i>GRP</i>	BMI	T	0.022	-0.0093	0.0191	0.6257	-0.0568	0.0388	0.1435	-0.0065	0.0393	0.8683	0.0346	0.0351	0.3252	
rs758747	<i>NLRC3</i>	BMI	T	0.023	-0.01	0.0165	0.5441	-0.0273	0.0335	0.4144	0.0099	0.0338	0.7691	-0.0248	0.0301	0.4094	
rs7599312	<i>ERBB4</i>	BMI	G	0.022	-0.0365	0.0161	0.02344	-0.0283	0.0328	0.3883	-0.0576	0.033	0.08047	-0.0661	0.0292	0.02346	
rs7899106	<i>GRID1</i>	BMI	G	0.040	0	0.0342	0.9996	-0.0501	0.0719	0.4863	0.1066	0.0687	0.1208	-0.0322	0.0622	0.6048	
rs7903146	<i>TCF7L2</i>	BMI	C	0.023	-0.0427	0.018	0.01736	-0.1069	0.0346	0.001981	-0.0621	0.0374	0.09669	-0.0323	0.0313	0.3022	Yes*
rs9400239	<i>FOXO3</i>	BMI	C	0.019	-0.0232	0.0154	0.1325	-0.0074	0.0313	0.8122	-0.0487	0.0314	0.1209	-0.0216	0.028	0.4407	
rs9925964	<i>KAT8</i>	BMI	A	0.019	-0.0191	0.0151	0.2071	-0.0097	0.0313	0.7559	-0.0327	0.0309	0.2894	-0.0398	0.0276	0.1491	Yes†

BMI, body mass index; EA, effect allele; SA, sensitivity analysis; SNP, single nucleotide polymorphism; T2D; type 2 diabetes.

*Excluded in a sensitivity analysis in which loci that overlapped between the four metabolic traits were removed.

†Excluded in a sensitivity analysis in which SNPs associated with blood lipids (low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, total cholesterol, or triglycerides) at genome-wide significance were removed.

‡Adjusted for body mass index.

§The *BDNF* locus has been identified to be associated with smoking (PMID: 20418890). The SNP in this locus was excluded in a sensitivity analysis.

Table e-2. Mendelian randomization estimates of the associations between each genetically predicted risk factor and ischemic stroke and its subtypes in analyses using the inverse-variance weighted, weighted median, and MR-Egger regression methods

	All ischemic strokes (18,476 cases/37,296 controls)		Large artery stroke (2947 cases/35,498 controls)		Small vessel stroke (2757 cases/35,498 controls)		Cardioembolic stroke (3860 cases/35,498 controls)	
	OR (95% CI)*	p Value	OR (95% CI)*	p Value	OR (95% CI)*	p Value	OR (95% CI)*	p Value
Inverse-variance weighted								
Type 2 diabetes	1.12 (1.07–1.17)	3.0x10 ⁻⁶	1.28 (1.16–1.40)	3.3x10 ⁻⁷	1.21 (1.10–1.33)	8.9x10 ⁻⁵	1.06 (0.97–1.15)	0.17
Fasting glucose	1.12 (0.98–1.28)	0.09	1.42 (1.08–1.85)	0.01	1.09 (0.83–1.43)	0.54	1.01 (0.80–1.29)	0.91
Fasting insulin	1.03 (0.78–1.37)	0.82	1.42 (0.80–2.50)	0.23	1.15 (0.65–2.02)	0.64	0.83 (0.50–1.38)	0.48
Body mass index	1.11 (0.98–1.27)	0.11	1.25 (0.96–1.63)	0.10	1.00 (0.76–1.30)	0.99	1.16 (0.91–1.47)	0.22
Weighted median								
Type 2 diabetes	1.13 (1.04–1.22)	0.002	1.34 (1.16–1.56)	1.1x10 ⁻⁴	1.19 (1.01–1.40)	0.04	1.09 (0.95–1.25)	0.21
Fasting glucose	0.92 (0.74–1.13)	0.41	1.52 (0.94–2.46)	0.09	0.87 (0.57–1.33)	0.51	0.90 (0.64–1.26)	0.53
Fasting insulin	0.98 (0.64–1.50)	0.93	1.85 (0.76–4.51)	0.18	1.16 (0.55–2.61)	0.73	0.79 (0.38–1.64)	0.52
Body mass index	1.01 (0.81–1.24)	0.99	1.40 (0.89–2.21)	0.14	0.89 (0.55–1.44)	0.64	1.11 (0.74–1.66)	0.62
Penalized weighted median†								
Type 2 diabetes	1.12 (1.04–1.21)	0.003	1.31 (1.13–1.52)	2.8x10 ⁻⁴	1.19 (1.01–1.40)	0.04	1.08 (0.95–1.24)	0.25
Fasting glucose	0.92 (0.74–1.13)	0.41	1.89 (1.21–2.97)	0.005	0.87 (0.57–1.32)	0.50	0.89 (0.64–1.25)	0.52
Fasting insulin	0.98 (0.64–1.50)	0.94	2.01 (0.82–4.95)	0.13	1.16 (0.51–2.61)	0.72	0.84 (0.41–1.75)	0.65
Body mass index	1.01 (0.81–1.24)	0.99	1.41 (0.89–2.22)	0.15	0.89 (0.55–1.44)	0.64	1.12 (0.75–1.68)	0.57
MR-Egger regression‡								
Type 2 diabetes	1.07 (0.94–1.19)	0.30	1.25 (0.98–1.53)	0.08	1.12 (0.88–1.40)	0.33	1.01 (0.83–1.24)	0.90
Fasting glucose	0.80 (0.64–1.02)	0.13	1.15 (0.70–1.87)	0.66	0.67 (0.42–1.11)	0.17	0.80 (0.52–1.24)	0.32
Fasting insulin§	–	–	–	–	–	–	–	–
Body mass index	1.05 (0.75–1.44)	0.82	1.03 (0.53–1.98)	0.96	1.22 (0.61–2.33)	0.63	1.15 (0.64–2.03)	0.68

*The scaling of the odds ratios was one unit higher log-odds for type 2 diabetes and one standard deviation increase of fasting glucose, fasting insulin, and body mass index.

†A weighted median approach that downweights the contribution to the analysis of genetic variants with heterogeneous ratio estimates.

‡Confidence intervals were estimated using bootstrapping.

§MR-Egger regression estimates could not be identified because the SNPs had similar magnitudes of association with fasting insulin.

Table e-3. Mendelian randomization estimates (inverse-variance weighted method) of the associations between each genetically predicted risk factor and ischemic stroke and its subtypes in sensitivity analyses excluding pleiotropic loci

Sensitivity analysis excluding	All ischemic strokes (18 476 cases/37,296 controls)		Large artery stroke (2947 cases/35,498 controls)		Small vessel stroke (2757 cases/35,498 controls)		Cardioembolic stroke (3860 cases/35,498 controls)	
	OR (95% CI)*	<i>p</i> Value	OR (95% CI)*	<i>p</i> Value	OR (95% CI)*	<i>p</i> Value	OR (95% CI)*	<i>p</i> Value
<i>TCF7L2</i> locus†								
Type 2 diabetes	1.11 (1.06-1.17)	5.4x10 ⁻⁵	1.25 (1.13-1.39)	3.3x10 ⁻⁵	1.21 (1.09-1.35)	3.4x10 ⁻⁴	1.05 (0.95-1.15)	0.32
Fasting glucose	1.10 (0.96-1.26)	0.17	1.36 (1.03-1.78)	0.03	1.05 (0.80-1.38)	0.74	1.00 (0.79-1.28)	0.97
Fasting insulin	1.13 (0.85-1.50)	0.41	1.84 (1.03-3.30)	0.04	1.30 (0.72-2.33)	0.38	0.88 (0.53-1.48)	0.64
Body mass index	1.13 (0.99-1.29)	0.07	1.30 (1.00-1.70)	0.06	1.02 (0.78-1.33)	0.90	1.17 (0.93-1.49)	0.19
Loci overlapping between the four metabolic traits								
Type 2 diabetes	1.11 (1.04-1.20)	0.003	1.32 (1.14-1.53)	2.5x10 ⁻⁴	1.23 (1.07-1.43)	0.005	1.05 (0.92-1.19)	0.50
Fasting glucose	1.09 (0.90-1.31)	0.37	1.04 (0.71-1.52)	0.84	0.95 (0.65-1.40)	0.81	1.05 (0.75-1.47)	0.78
Fasting insulin	1.01 (0.68-1.50)	0.97	2.07 (0.92-4.68)	0.08	1.27 (0.56-2.89)	0.56	0.81 (0.40-1.68)	0.58
Body mass index	1.13 (0.99-1.30)	0.07	1.33 (1.01-1.75)	0.04	1.03 (0.78-1.36)	0.84	1.19 (0.93-1.52)	0.16
Loci associated with lipids‡								
Type 2 diabetes	1.13 (1.07-1.18)	2.3x10 ⁻⁶	1.29 (1.17-1.42)	6.0x10 ⁻⁷	1.20 (1.09-1.33)	3.0x10 ⁻⁴	1.06 (0.97-1.16)	0.17
Fasting glucose	1.11 (0.97-1.28)	0.13	1.41 (1.07-1.86)	0.02	1.16 (0.87-1.53)	0.31	0.97 (0.75-1.24)	0.81
Fasting insulin	0.83 (0.57-1.23)	0.36	0.67 (0.30-1.47)	0.31	1.03 (0.47-2.30)	0.93	0.56 (0.28-1.12)	0.10
Body mass index	1.15 (0.99-1.34)	0.07	1.22 (0.89-1.65)	0.21	1.14 (0.84-1.55)	0.41	1.17 (0.89-1.54)	0.26
<i>BDNF</i> locus§								
Body mass index	1.09 (0.96-1.25)	0.19	1.23 (0.94-1.60)	0.14	0.98 (0.75-1.28)	0.86	1.14 (0.89-1.44)	0.30

CI, confidence interval; OR, odds ratio.

*The scaling of the odds ratios was one-unit higher log-odds for type 2 diabetes and one standard deviation increase of fasting glucose, fasting insulin, and body mass index.

†Excluding the *TCF7L2* locus, which is strongly associated with type 2 diabetes and also weakly with glucose, insulin, and body mass index.

‡Excluding single nucleotide polymorphisms associated with low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, total cholesterol, or triglycerides at genome-wide significance level in previous genome-wide association studies (PMID: 24097068, 20686565).

§Excluding the *BDNF* locus, which has been identified to be associated with smoking (PMID: 20418890) and also with body mass index.