

## **SUPPLEMENTARY MATERIALS**

**Supplementary Table I.** Effect estimates of the associations between genetic instruments of smoking and stroke

**Supplementary Table II.** The effect estimates for the associations of smoking with stroke after excluding the invalid instruments using the IVW method.

**Supplementary Table III.** Associations between smoking-associated loci and other traits from the GWAS catalog.

**Members of MEGASTROKE consortium**

**Supplementary Table I.** Effect estimates of the associations between genetic instruments of smoking and stroke

SNP	Chr	Pos	EA	SNP - smoking <sup>*</sup>		SNP - IS <sup>†</sup>			SNP - LV-IS <sup>†</sup>			SNP - CE-IS <sup>†</sup>			SNP - SV-IS <sup>†</sup>		
				$\beta$	SE	$\beta$	SE	<i>P</i>	$\beta$	SE	<i>P</i>	$\beta$	SE	<i>P</i>	$\beta$	SE	<i>P</i>
rs10030552	4	140972264	A	0.015	0.002	-0.009	0.012	0.480	-0.035	0.031	0.260	0.020	0.023	0.389	-0.003	0.028	0.917
rs1004787	2	45159091	A	0.018	0.002	-0.013	0.010	0.202	-0.005	0.025	0.857	-0.027	0.020	0.168	-0.002	0.024	0.941
rs10268837	7	3467366	T	0.016	0.002	0.007	0.010	0.503	0.001	0.025	0.971	0.019	0.020	0.329	-0.017	0.023	0.477
rs10461104	4	27490579	A	0.013	0.002	-0.012	0.010	0.243	-0.029	0.026	0.268	0.003	0.020	0.902	-0.016	0.024	0.505
rs10756197	9	11178030	A	0.012	0.002	0.009	0.010	0.365	0.004	0.025	0.867	-0.008	0.019	0.691	0.021	0.023	0.368
rs11065979	12	112059557	T	0.013	0.002	0.078	0.010	0.000	0.099	0.026	0.000	0.057	0.020	0.004	0.107	0.024	0.000
rs11134672	5	170395820	A	0.014	0.002	0.013	0.011	0.244	-0.017	0.026	0.508	0.014	0.021	0.502	0.061	0.025	0.014
rs11166986	8	141656155	A	0.012	0.002	-0.016	0.010	0.104	-0.018	0.025	0.459	-0.039	0.020	0.045	-0.023	0.023	0.326
rs1174864	7	53127559	A	0.012	0.002	-0.024	0.010	0.018	0.012	0.025	0.632	-0.025	0.019	0.190	-0.044	0.023	0.062
rs11808210	1	227515049	A	0.022	0.004	-0.019	0.019	0.332	-0.027	0.049	0.585	-0.013	0.039	0.742	-0.080	0.047	0.087
rs12030183	1	41761220	T	0.015	0.002	-0.007	0.010	0.492	0.006	0.026	0.833	-0.027	0.020	0.184	-0.008	0.024	0.747
rs12042107	1	91196176	T	0.014	0.002	0.013	0.010	0.183	0.040	0.025	0.105	-0.007	0.019	0.737	0.004	0.023	0.866
rs12150718	18	42674461	T	0.012	0.002	-0.011	0.011	0.340	0.001	0.028	0.970	-0.041	0.022	0.063	0.001	0.026	0.979
rs12153007	5	51026503	T	0.020	0.004	-0.004	0.017	0.798	0.010	0.042	0.802	0.008	0.033	0.801	-0.018	0.039	0.652
rs12476173	2	118247714	A	0.012	0.002	-0.004	0.010	0.720	0.008	0.026	0.768	0.004	0.020	0.834	-0.001	0.024	0.961
rs12662631	6	93842446	T	0.012	0.002	0.009	0.011	0.401	-0.002	0.027	0.950	0.050	0.021	0.016	0.013	0.025	0.610
rs12690535	2	226259373	A	0.016	0.003	0.009	0.013	0.484	-0.036	0.032	0.260	0.029	0.025	0.252	0.038	0.030	0.213
rs12757183	1	216920373	T	0.014	0.003	0.021	0.013	0.112	-0.065	0.032	0.043	0.014	0.025	0.587	0.010	0.030	0.732
rs12787182	11	59190811	A	0.013	0.002	-0.001	0.011	0.916	-0.016	0.027	0.562	-0.019	0.021	0.354	-0.004	0.025	0.891
rs12895462	14	77615441	T	0.014	0.003	0.002	0.013	0.868	0.044	0.032	0.167	0.004	0.025	0.880	-0.040	0.029	0.168
rs12930834	16	72951627	A	0.014	0.002	0.011	0.012	0.350	0.089	0.031	0.004	-0.010	0.023	0.663	0.006	0.028	0.844
rs13160204	5	157734762	A	0.012	0.002	-0.029	0.011	0.008	-0.035	0.027	0.191	-0.056	0.021	0.008	0.008	0.025	0.752
rs13187930	5	60384171	T	0.014	0.002	0.004	0.011	0.712	-0.014	0.028	0.624	0.011	0.022	0.618	0.013	0.026	0.631
rs13258512	8	92777433	A	0.015	0.002	0.002	0.010	0.862	0.001	0.025	0.978	0.008	0.019	0.679	-0.024	0.023	0.288
rs13357015	5	80263403	A	0.014	0.002	0.016	0.011	0.117	0.017	0.026	0.517	0.011	0.020	0.584	0.046	0.024	0.056
rs1368550	2	104078655	T	0.019	0.002	0.016	0.010	0.102	0.063	0.025	0.010	0.003	0.019	0.870	-0.004	0.023	0.878
rs1435741	15	47935843	A	0.016	0.002	0.010	0.010	0.346	0.058	0.025	0.019	0.011	0.019	0.572	-0.035	0.023	0.136
rs146127221	10	87465134	T	0.042	0.008	-0.020	0.036	0.579	-0.054	0.098	0.583	0.002	0.075	0.984	0.122	0.084	0.148

rs1549214	5	166997007	T	0.016	0.002	-0.007	0.010	0.483	0.019	0.026	0.475	0.013	0.020	0.529	0.016	0.024	0.512
rs16951001	15	67854241	T	0.012	0.002	0.018	0.010	0.072	0.013	0.025	0.621	0.013	0.020	0.492	0.048	0.024	0.043
rs17496618	2	44185718	T	0.019	0.003	0.011	0.018	0.524	0.079	0.044	0.074	-0.014	0.034	0.685	-0.035	0.038	0.352
rs17733784	18	53719925	T	0.013	0.002	0.011	0.010	0.272	0.029	0.026	0.264	0.041	0.020	0.041	-0.003	0.024	0.917
rs1919621	3	34421745	A	0.014	0.002	-0.003	0.010	0.737	-0.013	0.025	0.591	0.003	0.019	0.896	0.019	0.024	0.412
rs2185913	10	115410234	T	0.012	0.002	0.006	0.011	0.576	0.039	0.028	0.168	0.033	0.022	0.133	0.004	0.026	0.883
rs2236941	3	50247824	T	0.012	0.002	0.024	0.010	0.023	0.068	0.026	0.008	0.019	0.020	0.339	0.022	0.024	0.346
rs2291256	12	133393323	T	0.021	0.003	0.035	0.020	0.088	0.021	0.052	0.678	0.053	0.041	0.199	0.006	0.047	0.905
rs2585817	11	28602221	A	0.015	0.002	0.018	0.011	0.092	0.040	0.025	0.119	0.015	0.020	0.441	0.011	0.024	0.654
rs26251	5	106837450	T	0.013	0.002	-0.008	0.011	0.457	-0.022	0.026	0.400	-0.021	0.023	0.353	0.006	0.025	0.803
rs2633725	3	53751742	T	0.015	0.003	-0.008	0.014	0.584	-0.015	0.035	0.676	-0.006	0.028	0.844	-0.020	0.033	0.552
rs2783130	13	80170160	A	0.011	0.002	0.019	0.010	0.062	0.027	0.025	0.271	0.002	0.019	0.912	0.000	0.023	0.997
rs28527775	10	125700548	A	0.014	0.002	-0.007	0.011	0.560	0.001	0.029	0.966	-0.014	0.022	0.525	0.013	0.026	0.615
rs28647734	9	137977033	A	0.017	0.003	0.006	0.013	0.656	0.020	0.032	0.532	0.031	0.025	0.216	0.041	0.030	0.175
rs34495106	3	85651136	A	0.021	0.002	0.011	0.010	0.288	0.062	0.025	0.015	0.018	0.020	0.346	0.012	0.024	0.613
rs3783177	13	101151360	T	0.014	0.002	-0.008	0.012	0.521	-0.052	0.029	0.077	0.007	0.023	0.769	-0.025	0.028	0.358
rs42417	5	94198290	T	0.016	0.002	0.001	0.011	0.912	-0.007	0.028	0.811	0.008	0.021	0.709	-0.004	0.026	0.874
rs4479577	3	5723818	T	0.012	0.002	0.003	0.010	0.753	0.036	0.025	0.153	0.010	0.019	0.615	-0.032	0.024	0.180
rs4650277	1	74993721	A	0.015	0.002	-0.011	0.010	0.276	-0.029	0.025	0.249	-0.026	0.019	0.171	-0.011	0.024	0.638
rs4664442	2	162828001	A	0.016	0.002	-0.020	0.010	0.047	-0.007	0.025	0.771	-0.024	0.019	0.216	-0.039	0.023	0.088
rs4771948	13	97087892	T	0.011	0.002	0.009	0.011	0.399	0.039	0.026	0.132	-0.025	0.020	0.230	0.001	0.024	0.982
rs4790870	17	1970201	A	0.013	0.002	0.007	0.010	0.510	-0.008	0.025	0.743	-0.008	0.019	0.687	0.010	0.024	0.687
rs479971	12	69672471	A	0.015	0.002	-0.016	0.011	0.151	0.002	0.028	0.941	0.015	0.021	0.475	-0.033	0.026	0.200
rs4814884	20	19663293	T	0.012	0.002	0.024	0.010	0.016	0.034	0.025	0.173	0.010	0.020	0.600	-0.028	0.024	0.230
rs4888444	16	75690279	A	0.026	0.005	-0.034	0.027	0.197	-0.118	0.067	0.079	-0.125	0.054	0.021	0.014	0.063	0.828
rs5003492	8	93195529	A	0.013	0.002	0.001	0.010	0.951	-0.011	0.025	0.671	0.010	0.019	0.595	-0.007	0.023	0.759
rs525444	12	114110961	T	0.015	0.003	-0.018	0.013	0.160	-0.064	0.033	0.056	-0.039	0.024	0.107	0.006	0.029	0.831
rs550677	12	125811056	A	0.011	0.002	0.015	0.011	0.185	0.009	0.027	0.728	0.018	0.020	0.380	0.040	0.024	0.095
rs553785	1	96895325	A	0.012	0.002	-0.014	0.010	0.148	-0.040	0.024	0.097	0.003	0.019	0.890	-0.004	0.023	0.852
rs55921136	1	210359333	T	0.016	0.003	0.003	0.012	0.840	0.005	0.031	0.860	-0.022	0.023	0.350	-0.002	0.028	0.946
rs55974445	4	147893585	T	0.017	0.002	-0.006	0.011	0.581	-0.032	0.028	0.247	-0.006	0.021	0.768	-0.005	0.025	0.830

rs56081685	13	59454140	T	0.013	0.002	-0.003	0.011	0.789	-0.012	0.028	0.662	-0.033	0.022	0.127	-0.006	0.026	0.834
rs58695218	7	39432330	A	0.015	0.003	-0.013	0.013	0.302	0.015	0.031	0.641	-0.006	0.024	0.815	-0.005	0.029	0.867
rs6061162	20	29893501	T	0.020	0.003	0.000	0.018	0.986	0.022	0.045	0.619	0.051	0.036	0.152	-0.007	0.042	0.864
rs6119897	20	31145415	A	0.016	0.002	-0.008	0.012	0.479	-0.005	0.028	0.871	-0.023	0.022	0.302	0.042	0.026	0.109
rs6452791	5	87771093	A	0.012	0.002	0.018	0.010	0.075	0.031	0.024	0.209	0.047	0.019	0.013	-0.012	0.023	0.606
rs663175	11	121533827	A	0.013	0.002	-0.007	0.011	0.522	0.021	0.025	0.403	-0.011	0.019	0.573	-0.004	0.024	0.871
rs7130826	11	17037793	T	0.013	0.002	-0.013	0.011	0.240	-0.039	0.028	0.156	-0.052	0.022	0.016	0.017	0.026	0.502
rs71367545	18	77576337	A	0.016	0.003	0.002	0.014	0.888	0.011	0.034	0.739	0.024	0.028	0.389	0.027	0.031	0.383
rs7203668	16	76462582	A	0.012	0.002	0.027	0.010	0.007	0.035	0.025	0.151	0.025	0.019	0.191	-0.005	0.023	0.845
rs745570	17	77781725	A	0.011	0.002	0.002	0.010	0.873	-0.015	0.025	0.541	0.026	0.020	0.193	0.039	0.022	0.082
rs7645872	3	25209801	T	0.012	0.002	-0.010	0.010	0.299	-0.038	0.025	0.127	-0.010	0.019	0.614	-0.026	0.023	0.274
rs78058594	11	132280286	A	0.028	0.005	0.006	0.023	0.805	-0.045	0.061	0.459	0.013	0.046	0.785	0.089	0.058	0.125
rs8047834	16	25371716	A	0.012	0.002	0.006	0.011	0.602	0.002	0.027	0.931	0.004	0.021	0.858	0.004	0.025	0.874
rs883403	7	99047978	T	0.017	0.003	0.028	0.014	0.046	0.003	0.036	0.943	0.024	0.027	0.385	0.002	0.032	0.952
rs905871	11	4661285	A	0.012	0.002	-0.005	0.011	0.647	0.043	0.027	0.113	0.007	0.021	0.727	-0.042	0.025	0.088
rs9395644	6	50923637	A	0.020	0.004	0.036	0.016	0.027	0.082	0.041	0.045	0.011	0.032	0.727	0.011	0.038	0.773
rs969650	9	109378080	T	0.012	0.002	0.001	0.011	0.905	-0.036	0.026	0.163	0.004	0.020	0.845	-0.020	0.024	0.400
rs10186534	2	80957117	T	0.013	0.002	-0.002	0.011	0.859	-0.036	0.026	0.167	-0.026	0.020	0.199	-0.017	0.024	0.499
rs1022261	4	35476300	A	0.011	0.002	0.021	0.010	0.036	0.047	0.025	0.059	0.012	0.019	0.537	0.010	0.023	0.661
rs1022898	13	97075261	A	0.012	0.002	0.011	0.011	0.299	0.027	0.026	0.308	-0.024	0.021	0.239	0.006	0.025	0.799
rs10252114	7	121955468	T	0.012	0.002	0.012	0.010	0.259	0.017	0.026	0.505	0.022	0.020	0.266	0.001	0.024	0.969
rs10279261	7	133589846	A	0.011	0.002	-0.003	0.010	0.788	-0.003	0.025	0.920	0.018	0.020	0.374	0.032	0.024	0.180
rs10751226	11	73312252	T	0.015	0.003	0.012	0.014	0.392	-0.007	0.036	0.837	0.023	0.027	0.397	0.057	0.033	0.081
rs10914684	1	33795572	A	0.015	0.002	0.006	0.010	0.556	0.017	0.026	0.509	-0.009	0.020	0.660	0.042	0.024	0.083
rs10952199	7	1665339	T	0.014	0.002	-0.012	0.011	0.235	-0.002	0.027	0.947	0.001	0.020	0.944	-0.044	0.024	0.069
rs10970595	9	31910764	T	0.019	0.003	-0.019	0.016	0.222	0.011	0.040	0.790	-0.021	0.031	0.496	-0.035	0.037	0.342
rs11066971	12	114602860	T	0.017	0.003	-0.020	0.014	0.163	-0.018	0.036	0.611	-0.028	0.027	0.305	-0.057	0.033	0.081
rs1109480	12	121083279	A	0.014	0.002	-0.007	0.010	0.493	-0.012	0.026	0.630	-0.024	0.020	0.231	0.008	0.024	0.733
rs11165528	1	96432794	T	0.013	0.002	0.003	0.010	0.767	0.035	0.024	0.149	-0.009	0.019	0.652	-0.014	0.023	0.550
rs11210892	1	44100084	A	0.016	0.002	0.017	0.011	0.117	0.071	0.029	0.013	0.034	0.021	0.112	0.003	0.026	0.896
rs11255908	10	8802912	T	0.015	0.002	-0.007	0.012	0.563	-0.014	0.029	0.632	-0.010	0.023	0.674	-0.055	0.027	0.042

rs11771982	7	132302248	T	0.016	0.003	0.000	0.014	0.977	0.010	0.035	0.777	0.029	0.028	0.300	-0.031	0.033	0.345
rs11779675	8	10838461	A	0.013	0.002	0.008	0.011	0.465	0.005	0.026	0.840	0.014	0.021	0.508	0.037	0.025	0.133
rs11783093	8	27425349	T	0.026	0.003	-0.001	0.014	0.955	0.025	0.034	0.470	0.032	0.027	0.233	0.044	0.032	0.171
rs11844846	14	29487668	A	0.013	0.002	-0.024	0.011	0.023	-0.044	0.026	0.098	-0.028	0.019	0.139	-0.019	0.025	0.437
rs11872397	18	72535282	A	0.015	0.002	-0.014	0.012	0.249	0.002	0.029	0.956	0.005	0.023	0.826	0.024	0.028	0.382
rs12022778	1	50603995	A	0.016	0.002	-0.006	0.012	0.645	0.027	0.030	0.366	-0.007	0.024	0.763	-0.006	0.028	0.831
rs12053870	3	118302515	T	0.011	0.002	0.007	0.010	0.489	-0.014	0.025	0.581	0.002	0.019	0.935	0.038	0.023	0.100
rs12211126	6	67549451	T	0.012	0.002	0.005	0.010	0.621	0.035	0.025	0.163	-0.007	0.019	0.717	0.030	0.024	0.207
rs1221976	18	49996136	A	0.014	0.002	0.005	0.011	0.653	0.022	0.028	0.437	0.034	0.020	0.090	-0.017	0.025	0.503
rs12456711	18	280897	A	0.014	0.002	-0.018	0.012	0.131	-0.025	0.029	0.391	-0.044	0.023	0.053	-0.037	0.027	0.181
rs1246265	9	86761745	T	0.016	0.002	0.013	0.011	0.253	0.031	0.027	0.264	-0.013	0.021	0.548	0.003	0.025	0.903
rs12517438	5	30842054	T	0.011	0.002	-0.014	0.010	0.163	-0.028	0.025	0.252	-0.005	0.019	0.778	-0.019	0.023	0.407
rs12535004	7	114947112	T	0.015	0.003	0.000	0.011	0.993	-0.033	0.028	0.251	-0.028	0.022	0.198	0.094	0.026	0.000
rs1271272	2	207955477	A	0.012	0.002	-0.017	0.011	0.116	0.015	0.027	0.587	-0.040	0.021	0.051	-0.021	0.025	0.394
rs12997449	2	179039572	A	0.018	0.003	-0.004	0.016	0.805	0.012	0.039	0.755	0.010	0.031	0.754	0.049	0.036	0.173
rs13396935	2	653195	A	0.019	0.003	0.005	0.013	0.729	0.027	0.033	0.414	-0.012	0.026	0.638	0.010	0.031	0.740
rs1353911	3	117777904	A	0.025	0.003	0.019	0.014	0.174	0.014	0.034	0.677	0.007	0.027	0.785	0.089	0.033	0.006
rs1373129	9	102153698	A	0.013	0.002	0.021	0.010	0.040	0.042	0.024	0.086	0.013	0.019	0.487	-0.023	0.023	0.305
rs1469908	16	69764412	T	0.014	0.002	-0.006	0.010	0.558	-0.017	0.025	0.499	-0.041	0.020	0.037	0.033	0.024	0.167
rs1491617	4	173033976	T	0.013	0.002	0.011	0.011	0.279	0.018	0.027	0.497	0.044	0.020	0.027	0.029	0.024	0.235
rs16972552	16	73810454	C	0.018	0.003	-0.012	0.016	0.463	0.035	0.040	0.378	-0.008	0.032	0.800	0.032	0.038	0.404
rs17049905	2	59301572	A	0.020	0.003	0.010	0.018	0.581	0.037	0.040	0.349	-0.002	0.032	0.947	-0.050	0.038	0.188
rs17151637	8	10153082	T	0.015	0.002	0.000	0.011	0.986	0.005	0.027	0.854	-0.024	0.021	0.252	0.023	0.025	0.370
rs17348216	5	103924374	T	0.016	0.003	-0.010	0.013	0.446	0.005	0.032	0.871	-0.031	0.025	0.219	0.071	0.031	0.019
rs17657924	7	96625589	A	0.013	0.002	-0.002	0.011	0.844	0.019	0.027	0.487	0.032	0.021	0.121	-0.029	0.025	0.238
rs176644	15	89913632	T	0.012	0.002	-0.008	0.010	0.464	-0.029	0.026	0.256	-0.005	0.020	0.788	-0.030	0.024	0.215
rs1775370	1	72992856	T	0.014	0.002	-0.006	0.012	0.593	0.007	0.029	0.810	-0.025	0.023	0.273	-0.029	0.027	0.294
rs1891196	1	208718672	A	0.012	0.002	-0.004	0.010	0.671	0.013	0.025	0.599	0.022	0.020	0.249	-0.016	0.025	0.517
rs2202237	17	50208784	T	0.013	0.002	0.008	0.010	0.406	-0.046	0.025	0.071	0.043	0.019	0.026	-0.034	0.024	0.155
rs2310752	1	66392405	A	0.015	0.002	0.014	0.010	0.163	0.007	0.025	0.771	0.025	0.019	0.198	-0.009	0.023	0.712
rs2340403	1	73835777	T	0.014	0.002	0.006	0.010	0.570	0.018	0.025	0.476	-0.001	0.019	0.959	0.031	0.023	0.181

rs2358443	2	174930016	T	0.011	0.002	-0.025	0.010	0.016	0.007	0.025	0.786	-0.027	0.019	0.161	-0.066	0.023	0.005
rs239245	6	101090377	A	0.011	0.002	-0.008	0.010	0.426	0.018	0.025	0.459	0.029	0.019	0.132	0.015	0.023	0.521
rs240955	6	111660643	A	0.026	0.003	-0.010	0.013	0.459	0.030	0.032	0.349	-0.001	0.025	0.977	0.009	0.030	0.775
rs2419903	2	60528052	T	0.014	0.002	0.007	0.010	0.485	0.011	0.025	0.658	-0.019	0.019	0.337	-0.035	0.023	0.137
rs2652434	2	155742894	T	0.011	0.002	0.025	0.010	0.012	0.038	0.025	0.124	0.005	0.019	0.778	0.010	0.023	0.672
rs28459916	4	80330743	A	0.017	0.003	0.016	0.015	0.278	0.029	0.036	0.424	0.043	0.029	0.137	0.015	0.035	0.676
rs2866724	16	13760152	A	0.014	0.002	0.000	0.011	0.985	-0.010	0.028	0.712	0.003	0.022	0.886	0.040	0.026	0.128
rs288175	5	107352079	A	0.012	0.002	0.015	0.010	0.126	0.022	0.027	0.417	0.006	0.021	0.780	0.084	0.025	0.001
rs2939756	11	41436297	A	0.012	0.002	0.017	0.010	0.084	0.025	0.025	0.322	0.005	0.019	0.805	0.032	0.024	0.177
rs301805	1	8481016	T	0.011	0.002	0.021	0.010	0.041	0.039	0.025	0.115	0.041	0.020	0.036	-0.019	0.024	0.431
rs3026629	22	38329285	A	0.012	0.002	0.006	0.010	0.556	0.017	0.026	0.513	0.016	0.020	0.430	0.025	0.024	0.305
rs35875412	6	28331818	T	0.014	0.003	0.005	0.013	0.684	-0.052	0.030	0.088	0.046	0.025	0.062	0.008	0.028	0.770
rs35891966	11	20129311	A	0.024	0.004	0.004	0.028	0.890	0.005	0.074	0.942	0.024	0.055	0.661	0.019	0.061	0.761
rs3800227	6	108994161	A	0.013	0.002	-0.008	0.011	0.488	-0.004	0.028	0.897	-0.016	0.022	0.465	-0.049	0.026	0.057
rs3818987	6	37484606	T	0.014	0.002	0.020	0.010	0.048	-0.033	0.025	0.188	0.000	0.019	0.994	0.016	0.023	0.483
rs3851186	11	85931325	T	0.015	0.003	0.003	0.012	0.829	0.013	0.030	0.677	0.035	0.024	0.142	-0.036	0.028	0.193
rs3980078	2	113328043	A	0.016	0.003	0.028	0.013	0.026	-0.016	0.032	0.612	0.003	0.024	0.903	0.073	0.030	0.013
rs4543592	9	3014254	T	0.013	0.002	-0.007	0.010	0.503	-0.035	0.027	0.199	-0.025	0.019	0.192	0.032	0.023	0.170
rs4680392	3	157404329	T	0.014	0.002	-0.009	0.011	0.389	0.009	0.027	0.749	-0.017	0.021	0.418	0.018	0.025	0.471
rs4737525	8	59799781	A	0.013	0.002	0.017	0.010	0.084	0.015	0.025	0.542	-0.015	0.019	0.443	-0.012	0.023	0.591
rs4748779	10	22288132	T	0.014	0.002	-0.017	0.011	0.120	-0.002	0.028	0.930	-0.043	0.022	0.049	-0.030	0.026	0.250
rs4837631	9	122061948	T	0.013	0.002	0.006	0.010	0.533	-0.031	0.025	0.200	0.018	0.019	0.337	-0.006	0.023	0.809
rs4949465	1	32178489	T	0.018	0.003	0.002	0.014	0.893	-0.039	0.036	0.278	0.036	0.028	0.191	-0.006	0.034	0.854
rs4984916	16	749057	A	0.017	0.002	-0.012	0.012	0.322	-0.052	0.030	0.079	-0.016	0.023	0.496	0.009	0.029	0.760
rs55646170	1	99455931	T	0.022	0.004	0.032	0.018	0.079	0.045	0.045	0.319	0.044	0.035	0.213	0.014	0.042	0.738
rs58400863	4	31184484	A	0.014	0.002	-0.006	0.011	0.589	-0.014	0.027	0.615	0.004	0.021	0.838	-0.042	0.025	0.093
rs6059913	20	33143288	A	0.012	0.002	0.002	0.010	0.812	0.004	0.025	0.881	0.028	0.019	0.149	0.002	0.023	0.944
rs6265	11	27679916	T	0.022	0.003	0.015	0.013	0.261	0.052	0.033	0.109	0.034	0.026	0.183	0.026	0.031	0.404
rs6438208	3	114170272	A	0.013	0.002	0.008	0.012	0.518	0.014	0.031	0.659	0.026	0.024	0.287	0.011	0.028	0.707
rs6598539	15	99204483	T	0.013	0.002	0.013	0.010	0.209	0.010	0.025	0.703	0.022	0.019	0.252	0.006	0.023	0.794
rs6676022	1	154162503	T	0.022	0.003	0.020	0.015	0.187	0.014	0.038	0.720	0.020	0.030	0.500	0.060	0.036	0.098

rs6720647	2	137615688	A	0.014	0.002	0.003	0.012	0.778	0.005	0.030	0.861	0.028	0.023	0.229	-0.015	0.028	0.585
rs6965740	7	117514840	T	0.014	0.002	0.008	0.010	0.409	-0.003	0.025	0.891	-0.001	0.019	0.971	0.008	0.023	0.740
rs6971782	7	70526891	T	0.012	0.002	0.010	0.011	0.349	-0.027	0.027	0.308	0.002	0.021	0.924	0.004	0.025	0.858
rs7092200	10	104844872	T	0.020	0.002	0.010	0.010	0.336	-0.058	0.026	0.023	-0.012	0.019	0.536	0.007	0.023	0.778
rs7160389	14	98650988	T	0.012	0.002	0.021	0.010	0.039	-0.019	0.025	0.451	-0.001	0.019	0.980	0.060	0.024	0.011
rs72678864	4	112422145	A	0.018	0.003	-0.001	0.014	0.957	0.030	0.035	0.394	-0.057	0.027	0.038	-0.014	0.032	0.654
rs72733235	9	38275772	T	0.017	0.003	0.023	0.014	0.095	0.042	0.034	0.224	0.045	0.023	0.051	0.028	0.032	0.390
rs7295765	12	86459040	A	0.015	0.003	0.018	0.013	0.163	-0.022	0.032	0.491	0.017	0.025	0.500	0.072	0.029	0.014
rs7333559	13	100546450	A	0.016	0.003	0.002	0.013	0.892	-0.010	0.033	0.760	0.011	0.025	0.674	0.015	0.030	0.611
rs7575189	2	174015168	A	0.011	0.002	0.004	0.010	0.677	-0.011	0.025	0.664	0.013	0.019	0.489	0.012	0.023	0.617
rs76608582	19	4474725	A	0.033	0.005	0.014	0.028	0.612	0.035	0.080	0.664	-0.001	0.057	0.991	0.030	0.071	0.667
rs772921	12	56403577	T	0.012	0.002	-0.003	0.011	0.769	0.018	0.026	0.493	-0.015	0.023	0.522	-0.001	0.025	0.977
rs7754741	6	98749329	T	0.015	0.002	-0.005	0.011	0.655	-0.015	0.028	0.581	-0.031	0.021	0.143	0.019	0.026	0.463
rs78175438	21	40663255	T	0.019	0.003	0.024	0.016	0.131	-0.023	0.040	0.557	0.040	0.031	0.188	0.018	0.036	0.614
rs7870475	9	128134034	T	0.013	0.002	0.009	0.010	0.362	0.022	0.025	0.365	0.011	0.019	0.571	-0.027	0.023	0.232
rs78954884	16	17956466	A	0.025	0.005	-0.058	0.033	0.077	-0.080	0.084	0.342	-0.067	0.063	0.285	-0.053	0.077	0.492
rs7901883	10	103186838	A	0.013	0.002	0.000	0.012	0.993	0.013	0.030	0.659	0.026	0.024	0.271	-0.023	0.028	0.425
rs7905987	10	63666637	A	0.018	0.002	0.006	0.010	0.583	0.013	0.025	0.617	0.009	0.019	0.625	-0.019	0.023	0.429
rs7938812	11	112911004	T	0.030	0.002	0.016	0.010	0.129	0.045	0.026	0.083	0.006	0.020	0.779	0.035	0.024	0.140
rs9329342	10	13532648	T	0.011	0.002	0.023	0.010	0.026	0.046	0.026	0.070	0.058	0.020	0.003	0.032	0.024	0.178
rs9388686	6	129425564	A	0.014	0.003	0.013	0.013	0.323	0.061	0.033	0.062	0.011	0.025	0.669	-0.004	0.030	0.894
rs9571576	13	66936133	T	0.011	0.002	-0.016	0.010	0.110	-0.006	0.025	0.803	-0.030	0.019	0.122	-0.020	0.023	0.397
rs961414	2	146113733	T	0.022	0.002	-0.002	0.010	0.883	0.014	0.025	0.586	0.002	0.019	0.927	0.005	0.023	0.824
rs962472	10	56700597	T	0.012	0.002	-0.006	0.010	0.553	-0.013	0.025	0.614	-0.021	0.019	0.288	-0.003	0.023	0.883

abbreviations: CE-IS, cardioembolic ischemic stroke; Chr, chromosome; EA, effect allele; IS, ischemic stroke; LV-IS, large artery ischemic stroke; Pos, position; SE, standard error; SNP, single nucleotide polymorphism; SV-IS, small vessel ischemic stroke.

\* Results ( $\beta$  and SE) were derived from a genome-wide association study of smoking (ever smoker vs. never smoker).

† Results ( $\beta$ , SE and  $P$ ) were derived from the MEGASTROKE consortium.

**Supplementary Table II.** The effect estimates for the associations of smoking with ischemic stroke after excluding the invalid instruments using the IVW method.

Outcomes	Number of SNPs	OR	95% CI	<i>P</i> -value
Ischemic stroke	171	1.19	1.06-1.34	0.003
Cardioembolic ischemic stroke	174	1.13	0.90-1.41	0.289
Small vessel ischemic stroke	174	1.24	0.95-1.62	0.115

Abbreviations: CI, confidence interval; OR, odds ratio; SNP, single nucleotide polymorphism.



**Supplementary Table III.** Associations between smoking loci and other traits (from the GWAS catalog)\*

SNP	Chr	Trait (Reference)	P-value
rs11210892	1	Autism spectrum disorder <sup>1</sup>	$4 \times 10^{-10}$
		Schizophrenia <sup>2</sup>	$3 \times 10^{-10}$
rs12042107	1	Risky sexual behaviour measurement <sup>3</sup>	$9 \times 10^{-12}$
		Self reported educational attainment <sup>4</sup>	$7 \times 10^{-9}$
rs4664442	2	Intelligence <sup>5</sup>	$5 \times 10^{-17}$
rs72678864	4	Self reported educational attainment <sup>6</sup>	$2 \times 10^{-9}$
rs12517438	5	Well-being measurement <sup>7</sup>	$4 \times 10^{-8}$
rs11783093	8	Schizophrenia <sup>8</sup>	$8 \times 10^{-12}$
rs17151637	8	Mathematical ability <sup>6</sup>	$8 \times 10^{-11}$
rs35891966	11	Intelligence <sup>9</sup>	$1 \times 10^{-8}$
rs6265	11	Body mass index <sup>10</sup>	$2 \times 10^{-51}$
		Hip circumference <sup>11</sup>	$1 \times 10^{-14}$
rs11065979	12	Risk-taking behaviour <sup>3</sup>	$3 \times 10^{-10}$
		Alcohol drinking <sup>12</sup>	$2 \times 10^{-22}$
		Basophil count <sup>13</sup>	$1 \times 10^{-12}$
		Blood protein measurement <sup>14</sup>	$2 \times 10^{-12}$
		Diastolic blood pressure <sup>12</sup>	$2 \times 10^{-45}$
		Intraocular pressure measurement <sup>15</sup>	$3 \times 10^{-9}$
		Mean arterial pressure <sup>12</sup>	$2 \times 10^{-14}$
		Parental longevity <sup>16</sup>	$2 \times 10^{-12}$
		Primary biliary cirrhosis <sup>17</sup>	$3 \times 10^{-9}$
		Psoriasis <sup>18</sup>	$2 \times 10^{-8}$
rs772921	12	Systolic blood pressure <sup>12</sup>	$2 \times 10^{-22}$
		Heel bone mineral density <sup>19</sup>	$9 \times 10^{-10}$

rs7160389	14	Eosinophil count <sup>19</sup>	$3 \times 10^{-8}$
rs2202237	17	Blood protein measurement <sup>20</sup>	$5 \times 10^{-10}$
rs745570	17	Breast carcinoma <sup>21</sup>	$1 \times 10^{-9}$
rs76608582	19	Intelligence <sup>22</sup>	$3 \times 10^{-8}$
		Self-reported educational attainment <sup>19</sup>	$1 \times 10^{-9}$

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Abbreviations: Chr, chromosome; SNP, single nucleotide polymorphism.

\* SNPs associated with secondary traits according to previous genome-wide association studies.

Any ambiguities were not shown in this table.

### **Members of MEGASTROKE consortium**

We gratefully acknowledge the contributing studies and databases (MEGASTROKE project) that made GWAS summary data available. We acknowledge the contributions of Rainer Malik, Ganesh Chauhan, Matthew Traylor, Muralidharan Sargurupremraj, Yukinori Okada, Aniket Mishra, Loes Rutten-Jacobs, Anne-Katrin Giese, Sander W. van der Laan, Solveig Gretarsdottir, Christopher D. Anderson, Michael Chong, Hieab H. H. Adams, Tetsuro Ago, Peter Almgren, Philippe Amouyel, Hakan Ay, Traci M. Bartz, Oscar R. Benavente, Steve Bevan, Giorgio B. Boncoraglio, Robert D. Brown, Jr, Adam S. Butterworth, Caty Carrera, Cara L. Carty, Daniel I. Chasman, Wei-Min Chen, John W. Cole, Adolfo Correa, Ioana Cotlarciuc, Carlos Cruchaga, John Danesh, Paul I. W. de Bakker, Anita L. DeStefano, Marcel den Hoed, Qing Duan, Stefan T. Engelter, Guido J. Falcone, Rebecca F. Gottesman, Raji P. Grewal, Vilmundur Gudnason, Stefan Gustafsson, Jeffrey Haessler, Tamara B. Harris, Ahamad Hassan, Aki S. Havulinna, Susan R. Heckbert, Elizabeth G. Holliday, George Howard, Fang-Chi Hsu, Hyacinth I. Hyacinth, M. Arfan Ikram, Erik Ingelsson, Marguerite R. Irvin, Xueqiu Jian, Jordi Jimenez-Conde, Julie A. Johnson, J. Wouter Jukema, Masahiro Kanai, Keith L. Keene, Brett M. Kissela, Dawn O. Kleindorfer, Charles Kooperberg, Michiaki Kubo, Leslie A. Lange, Carl D. Langefeld, Claudia Langenberg, Lenore J. Launer, Jin-Moo Lee, Robin Lemmens, Didier Leys, Cathryn M. Lewis, Wei-Yu Lin, Arne G. Lindgren, Erik Lorentzen, Patrik K. Magnusson, Jane Maguire, Ani Manichaikul, Patrick F. McArdle, James F. Meschia, Braxton D. Mitchell, Thomas H. Mosley, Michael A. Nalls, Toshiharu Ninomiya, Martin J. O'Donnell, Bruce M. Psaty, Sara L. Pulit, Kristiina Rannikmäe, Alexander P. Reiner, Kathryn M. Rexrode, Kenneth Rice, Stephen S. Rich, Paul M. Ridker, Natalia S. Rost, Peter M. Rothwell, Jerome I. Rotter, Tatjana Rundek, Ralph L. Sacco, Saori Sakaue, Michele M. Sale, Veikko Salomaa, Bishwa R. Sapkota, Reinhold Schmidt, Carsten O. Schmidt, Ulf Schminke, Pankaj Sharma, Agnieszka Slowik, Cathie L. M. Sudlow, Christian Tanislav, Turgut Tatlisumak, Kent D. Taylor, Vincent N. S. Thijs, Gudmar Thorleifsson, Unnur Thorsteinsdottir, Steffen Tiedt, Stella Trompet, Christophe Tzourio, Cornelia M. van Duijn, Matthew Walters, Nicholas J. Wareham, Sylvia Wassertheil-Smoller, James G. Wilson, Kerri L. Wiggins, Qiong Yang, Salim Yusuf, AFGen Consortium, Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium, International Genomics of Blood Pressure (iGEN-BP) Consortium, INVENT Consortium, STARNET, Joshua C. Bis, Tomi Pastinen, Arno Ruusalepp, Eric E. Schadt, Simon Koplev, Johan L. M. Björkegren, Veronica Codoni, Mete Civelek, Nicholas L. Smith, David A. Tregouet, Ingrid E. Christophersen, Carolina Roselli, Steven A. Lubitz, Patrick T. Ellinor, E. Shyong Tai, Jaspal S. Kooner, Norihiro Kato, Jiang He, Pim van der Harst, Paul Elliott, John C. Chambers, Fumihiko Takeuchi, Andrew D. Johnson, BioBank Japan Cooperative Hospital Group, COMPASS Consortium, EPiC-CVD Consortium, EPiC-interAct Consortium, International Stroke Genetics Consortium (ISGC), METASTROKE Consortium, Neurology Working Group of the CHARGE

Consortium, NiNDS Stroke Genetics Network (SiGN), UK Young Lacunar DNA Study, MEGASTROKE Consortium, Dharambir K. Sanghera, Olle Melander, Christina Jern, Daniel Strbian, Israel Fernandez-Cadenas, W. T. Longstreth, Jr, Arndt Rolfs, Jun Hata, Daniel Woo, Jonathan Rosand, Guillaume Pare, Jemma C. Hopewell, Danish Saleheen, Kari Stefansson, Bradford B. Worrall, Steven J. Kittner, Sudha Seshadri, Myriam Fornage, Hugh S. Markus, Joanna M. M. Howson, Yoichiro Kamatani, Stephanie Debette, and Martin Dichgans.

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