WEB MATERIAL

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Web Table 1. List of the 210 SNPs that have been identified in three previous genome-wide association studies (GWAS) of cigarette smoking in studies of African Americans or multi-ethnic studies.

Paper	Smoking Variable	Chr	Gene	SNP	Coded Allele	*P*	Source
David SP et al. (2012) (9)	Cigarettes/day	15	*CHRNA5*	rs2036527	A	1.84E-08	Table 2
	Cigarettes/day	15	*CHRNA5*	rs667282	C	1.81E-07	Table 2
	Cigarettes/day	1	*C1orf100*	rs3101457	A	2.63E-07	Table 2
	Cigarettes/day	15	*CHRNA3*	rs938682	A	3.75E-07	Table 2
	Cigarettes/day	15	*LOC503519*	rs547843	C	6.16E-07	Table 2
	Cigarettes/day	15	*PSMA4*	rs3813570	C	9.85E-07	Table 2
	Age of smoking initiation	10	*SPOCK2*	rs1678618	A	8.25E-07	Table 2
	Age of smoking initiation	10	*SPOCK2*	rs1245577	C	8.30E-07	Table 2
	Age of smoking initiation	10	*SPOCK2*	rs1612028	C	9.28E-07	Table 2
Hamidovic A et al. (2011) (8)	Pack-years	11	*BDNFOS*	rs10767658	C	1.55E-07	Table 1
	Pack-years	11	*BDNFOS*	rs925946	G	1.64E-07	Table 1
	Pack-years	11	*BDNF*	rs1401635	C	4.71E-07	Table 1
	Pack-years	11	*BDNF*	rs11030108	A	7.81E-07	Table 1
	Pack-years	11	*BDNF*	rs11030119	A	1.35E-06	Table 1
	Pack-years	11	*BDNFOS*	rs17309874	A	1.89E-05	Table 1
	Pack-years	11	*BDNF*	rs1013402	A	2.49E-05	Table 1
	Pack-years	11	*BDNF*	rs10835211	A	2.56E-05	Table 1
	Pack-years	11	*BDNF*	rs11030107	A	2.60E-05	Table 1
	Pack-years	11	*BDNF*	rs11030102	C	2.62E-05	Table 1
	Pack-years	11		rs17309930	A	3.17E-05	Table 1
	Pack-years	11	*BDNF*	rs12273363	C	3.21E-05	Table 1
	Pack-years	11		rs12288512	A	3.23E-05	Table 1
	Pack-years	15	*PSMA4*	rs12915366	A	3.58E-05	Table 1
	Pack-years	15	*AGPHD1*	rs12910289	G	3.61E-05	Table 1
	Pack-years	15	*AGPHD1*	rs1504546	C	3.61E-05	Table 1
	Pack-years	15	*AGPHD1*	rs12906951	C	3.62E-05	Table 1

	Pack-years	15	*PSMA4*	rs3813572	C	3.62E-05	Table 1
	Pack-years	15	*AGPHD1*	rs11636131	C	3.63E-05	Table 1
	Pack-years	15	*AGPHD1*	rs11632604	C	3.64E-05	Table 1
	Pack-years	15	*PSMA4*	rs12916483	A	3.64E-05	Table 1
	Pack-years	15	*PSMA4*	rs3813571	G	4.14E-05	Table 1
	Pack-years	15	*PSMA4*	rs12916999	A	4.25E-05	Table 1
	Pack-years	15	*AGPHD1*	rs952216	C	7.61E-05	Table 1
	Pack-years	15	*CHRNA3*	rs12914385	C	7.62E-05	Table 1
Tobacco and Genetics Consortium (2010) (7)	Smoking initiation (ever vs. never)	11	*BDNF*	rs6265	T	1.72E-05	Table 2
	Smoking initiation (ever vs. never)	11	*BDNF*	rs1013442	T	3.39E-05	Table 2
	Smoking initiation (ever vs. never)	11	*BDNF*	rs4923457	T	2.08E-05	Table 2
	Smoking initiation (ever vs. never)	11	*BDNF*	rs4923460	T	2.22E-05	Table 2
	Smoking initiation (ever vs. never)	11	*BDNF*	rs4074134	T	1.90E-05	Table 2
	Smoking initiation (ever vs. never)	11	*BDNF*	rs1304100	G	4.86E-05	Table 2
	Smoking initiation (ever vs. never)	11	*BDNF*	rs6484320	T	2.04E-05	Table 2
	Smoking initiation (ever vs. never)	11	*BDNF*	rs879048	C	2.28E-05	Table 2
	smoking cessation (former vs current)	9	*DBH*	rs3025343	G	5.68E-06	Table 2
	Cigarettes/day	10	*LOC100188947*	rs1329650	T	2.33E-06	Table 2
	Cigarettes/day	10	*LOC100188947*	rs1028936	C	1.57E-06	Table 2
	Cigarettes/day	19	*EGLN2*	rs3733829	G	7.67E-05	Table 2
	Cigarettes/day	15	*CHRNA3*	rs1051730	G	8.00E-33	Table 2
	Cigarettes/day	15	*CHRNA5*	rs16969968	G	4.48E-33	Table 2
	Cigarettes/day	15	*CHRNA5*	rs684513	G	5.87E-25	Web Table 6

Cigarettes/day	15	*LOC123688*	rs9788682	G	2.44E-23	Web Table 6
Cigarettes/day	15	*LOC123688*	rs7163730	G	2.21E-24	Web Table 6
Cigarettes/day	15	*LOC123688*	rs7164594	T	3.10E-24	Web Table 6
Cigarettes/day	15	*CHRNA5*	rs667282	T	3.65E-24	Web Table 6
Cigarettes/day	15	*LOC123688*	rs4461039	T	2.59E-24	Web Table 6
Cigarettes/day	15	*LOC123688*	rs2036534	T	1.49E-23	Web Table 6
Cigarettes/day	15	*CHRNA3*	rs7177514	G	3.95E-25	Web Table 6
Cigarettes/day	15	*CHRNA3*	rs8042059	C	4.57E-25	Web Table 6
Cigarettes/day	15	*PSMA4*	rs3813570	T	1.24E-23	Web Table 6
Cigarettes/day	15	*CHRNA3*	rs11637630	G	3.95E-25	Web Table 6
Cigarettes/day	15	*CHRNA5*	rs637137	T	5.32E-24	Web Table 6
Cigarettes/day	15	*CHRNA3*	rs6495308	T	4.69E-25	Web Table 6
Cigarettes/day	15	*CHRNA3*	rs938682	G	1.76E-24	Web Table 6
Cigarettes/day	15	*CHRNA3*	rs12910984	G	1.84E-24	Web Table 6
Cigarettes/day	15	*CHRNA3*	rs3743078	G	4.22E-25	Web Table 6
Cigarettes/day	15	*CHRNA3*	rs8042374	G	2.38E-24	Web Table 6
Cigarettes/day	15	*IREB2*	rs2869030	T	3.52E-12	Web Table 6
Cigarettes/day	15	*CHRNA3*	rs4887069	G	6.52E-23	Web Table 6
Cigarettes/day	15	*CHRNA3 CHRNB4*	rs6495309	T	4.51E-23	Web Table 6
Cigarettes/day	15	*CHRNB4*	rs12440014	G	6.02E-24	Web Table 6
Cigarettes/day	15	*IREB2*	rs4887053	C	3.71E-19	Web Table 6
Cigarettes/day	15	*IREB2*	rs2869032	T	3.78E-19	Web Table 6
Cigarettes/day	15	*IREB2*	rs2869045	T	3.95E-19	Web Table 6
Cigarettes/day	15	*IREB2*	rs5019044	T	4.22E-20	Web Table 6
Cigarettes/day	15	*IREB2*	rs11072766	T	1.47E-18	Web Table 6
Cigarettes/day	15	*IREB2*	rs2938674	C	2.06E-18	Web Table 6
Cigarettes/day	15	*IREB2*	rs2568483	G	2.31E-18	Web Table 6
Cigarettes/day	15	*IREB2*	rs2568488	T	2.66E-18	Web Table 6
Cigarettes/day	15	*IREB2*	rs2656073	T	3.07E-18	Web Table 6
Cigarettes/day	15	*IREB2*	rs2656069	T	6.05E-18	Web Table 6
Cigarettes/day	15	*IREB2*	rs2656071	T	3.08E-18	Web Table 6

Cigarettes/day	15	*IREB2*	rs924840	T	3.54E-18	Web Table 6
Cigarettes/day	15	*IREB2*	rs2938671	G	3.70E-18	Web Table 6
Cigarettes/day	15	*IREB2*	rs2958719	G	9.62E-16	Web Table 6
Cigarettes/day	15	*CHRNB4*	rs12441088	T	7.60E-22	Web Table 6
Cigarettes/day	15	*CHRNA3*	rs12443170	G	7.34E-18	Web Table 6
Cigarettes/day	15	*CHRNB4*	rs11636605	G	8.58E-16	Web Table 6
Cigarettes/day	15	*CHRNB4*	rs11072768	T	2.18E-15	Web Table 6
Cigarettes/day	15	*CHRNB4*	rs12441998	G	2.45E-15	Web Table 6
Cigarettes/day	15	*CHRNB4*	rs1316971	G	3.37E-15	Web Table 6
Cigarettes/day	15	*CHRNA5*	rs569207	T	6.35E-06	Web Table 6
Cigarettes/day	15	*CHRNA3 CHRNB4*	rs11072774	T	1.99E-12	Web Table 6
Cigarettes/day	15	*CHRNB4*	rs9920506	G	7.08E-13	Web Table 6
Cigarettes/day	15	*CHRNA3 CHRNB4*	rs12594247	T	7.10E-12	Web Table 6
Cigarettes/day	15	*CHRNA3 CHRNB4*	rs4887074	G	9.47E-09	Web Table 6
Cigarettes/day	15	*CHRNA3 CHRNB4*	rs8023822	G	5.06E-09	Web Table 6
Cigarettes/day	15	*CHRNA3*	rs578776	G	2.68E-19	Web Table 6
Cigarettes/day	15	*CHRNB4*	rs16970006	T	6.55E-08	Web Table 6
Cigarettes/day	15	*CHRNA3 CHRNB4*	rs12148319	G	4.50E-09	Web Table 6
Cigarettes/day	15	*CHRNA5*	rs518425	G	2.11E-18	Web Table 6
Cigarettes/day	15	*CHRNA3 CHRNB4*	rs12594550	G	1.10E-08	Web Table 6
Cigarettes/day	15	*ADAMTS7*	rs11634628	G	4.03E-07	Web Table 6
Cigarettes/day	15	*ADAMTS7*	rs11072794	T	4.14E-07	Web Table 6
Cigarettes/day	15	*ADAMTS7*	rs12899940	T	4.31E-07	Web Table 6
Cigarettes/day	15	*IREB2*	rs4362358	T	4.11E-17	Web Table 6
Cigarettes/day	15	*ADAMTS7*	rs4887078	T	7.69E-07	Web Table 6
Cigarettes/day	15	*ADAMTS7*	rs11072793	G	8.17E-07	Web Table 6
Cigarettes/day	15	*IREB2*	rs1062980	T	5.98E-16	Web Table 6
Cigarettes/day	15	*IREB2*	rs12904234	T	6.09E-16	Web Table 6
Cigarettes/day	15	*PSMA4*	rs7173512	T	2.41E-05	Web Table 6
Cigarettes/day	15	*IREB2*	rs1964678	G	5.03E-16	Web Table 6
Cigarettes/day	15	*IREB2*	rs8042238	T	4.17E-16	Web Table 6

Cigarettes/day	15	*IREB2*	rs4299116	T	4.31E-16	Web Table 6
Cigarettes/day	15	*CHRNA3*	rs3743075	T	0.000084	Web Table 6
Cigarettes/day	15	*IREB2*	rs8043227	G	4.27E-16	Web Table 6
Cigarettes/day	15	*IREB2*	rs8042260	G	4.19E-16	Web Table 6
Cigarettes/day	15	*IREB2*	rs12910910	T	4.28E-16	Web Table 6
Cigarettes/day	15	*IREB2*	rs12903295	G	4.38E-16	Web Table 6
Cigarettes/day	15	*IREB2*	rs965604	G	4.51E-16	Web Table 6
Cigarettes/day	15	*IREB2*	rs13180	T	1.56E-15	Web Table 6
Cigarettes/day	15		rs11633519	G	9.16E-07	Web Table 6
Cigarettes/day	15	*CHRNB4*	rs8032552	T	4.10E-07	Web Table 6
Cigarettes/day	15	*CHRNB4*	rs8043123	T	4.96E-07	Web Table 6
Cigarettes/day	15	*CHRNB4*	rs11072787	T	2.64E-07	Web Table 6
Cigarettes/day	15	*CHRNA3*	rs12914385	T	4.23E-35	Web Table 6
Cigarettes/day	15	*ADAMTS7*	rs11629637	T	1.35E-20	Web Table 6
Cigarettes/day	15	*ADAMTS7*	rs11638490	T	6.65E-21	Web Table 6
Cigarettes/day	15		rs12910627	G	3.67E-21	Web Table 6
Cigarettes/day	15	*ADAMTS7*	rs899997	T	2.72E-06	Web Table 6
Cigarettes/day	15		rs11072791	C	5.04E-21	Web Table 6
Cigarettes/day	15	*CHRNA3 CHRNB4*	rs11634351	G	7.64E-25	Web Table 6
Cigarettes/day	15	*ADAMTS7*	rs1383634	T	3.18E-06	Web Table 6
Cigarettes/day	15	*ADAMTS7*	rs2219939	G	3.42E-06	Web Table 6
Cigarettes/day	15		rs922692	C	5.69E-21	Web Table 6
Cigarettes/day	15	*ADAMTS7*	rs4887091	T	4.95E-06	Web Table 6
Cigarettes/day	15	*CHRNB4*	rs11638372	T	6.77E-21	Web Table 6
Cigarettes/day	15	*CHRNB4*	rs11072785	T	7.69E-22	Web Table 6
Cigarettes/day	15	*CHRNB4*	rs1021071	G	7.06E-22	Web Table 6
Cigarettes/day	15	*CHRNB4*	rs4887077	T	7.64E-21	Web Table 6
Cigarettes/day	15	*ADAMTS7*	rs7182567	G	5.44E-06	Web Table 6
Cigarettes/day	15	*CHRNA3 CHRNB4*	rs11638830	G	3.46E-23	Web Table 6
Cigarettes/day	15	*CHRNB4*	rs12902602	G	6.97E-22	Web Table 6
Cigarettes/day	15	*CHRNB4*	rs4886580	T	8.96E-22	Web Table 6

Cigarettes/day	15	*CHRNA3 CHRNB4*	rs6495314	C	7.69E-23	Web Table 6
Cigarettes/day	15	*CHRNA3 CHRNB4*	rs1996371	T	4.35E-23	Web Table 6
Cigarettes/day	15	*CHRNA3 CHRNB4*	rs12899135	G	1.56E-22	Web Table 6
Cigarettes/day	15	*CHRNB4*	rs11639372	T	1.01E-21	Web Table 6
Cigarettes/day	15	*ADAMTS7*	rs3813565	T	3.26E-21	Web Table 6
Cigarettes/day	15	*ADAMTS7 MORF4L1*	rs7403393	G	1.57E-08	Web Table 6
Cigarettes/day	15	*ADAMTS7 MORF4L1*	rs7164529	G	4.39E-09	Web Table 6
Cigarettes/day	15	*ADAMTS7*	rs12286	G	1.06E-18	Web Table 6
Cigarettes/day	15	*MORF4L1*	rs12595538	T	7.80E-09	Web Table 6
Cigarettes/day	15	*ADAMTS7*	rs4887082	T	2.88E-19	Web Table 6
Cigarettes/day	15	*ADAMTS7*	rs1809420	T	3.23E-18	Web Table 6
Cigarettes/day	15	*ADAMTS7*	rs7174367	G	7.00E-18	Web Table 6
Cigarettes/day	15	*ADAMTS7 MORF4L1*	rs11072810	T	1.15E-08	Web Table 6
Cigarettes/day	15	*ADAMTS7 MORF4L1*	rs11072811	C	1.22E-08	Web Table 6
Cigarettes/day	15	*MORF4L1*	rs17243470	T	1.28E-07	Web Table 6
Cigarettes/day	15	*CHRNA3 CHRNB4*	rs17487514	T	3.25E-05	Web Table 6
Cigarettes/day	15	*ADAMTS7 MORF4L1*	rs4539564	G	1.91E-09	Web Table 6
Cigarettes/day	15	*ADAMTS7 MORF4L1*	rs11852830	T	6.16E-08	Web Table 6
Cigarettes/day	15	*CHRNB4*	rs11857532	T	6.35E-18	Web Table 6
Cigarettes/day	15	*ADAMTS7 MORF4L1*	rs8032771	G	5.54E-08	Web Table 6
Cigarettes/day	15	*CHRNA3*	rs8040868	T	4.03E-08	Web Table 6
Cigarettes/day	15	*ADAMTS7 MORF4L1*	rs8035039	G	3.12E-09	Web Table 6
Cigarettes/day	15	*ADAMTS7 MORF4L1*	rs6495337	G	1.55E-07	Web Table 6
Cigarettes/day	15	*ADAMTS7*	rs7171916	G	1.23E-14	Web Table 6
Cigarettes/day	15	*ADAMTS7 MORF4L1*	rs7173743	T	2.14E-08	Web Table 6
Cigarettes/day	15	*ADAMTS7 MORF4L1*	rs5029904	G	1.65E-07	Web Table 6
Cigarettes/day	15	*LOC123688*	rs931794	G	1.64E-31	Web Table 6
Cigarettes/day	15	*LOC123688*	rs8031948	T	3.15E-31	Web Table 6
Cigarettes/day	15	*LOC123688*	rs10519203	G	4.89E-31	Web Table 6
Cigarettes/day	15	*LOC123688*	rs9788721	T	4.14E-31	Web Table 6
Cigarettes/day	15	*CHRNA3 CHRNB4*	rs12910237	T	1.43E-07	Web Table 6

Cigarettes/day	15	*CHRNB4*	rs922691	G	6.04E-07	Web Table 6
Cigarettes/day	15	*IREB2*	rs1504550	G	4.53E-26	Web Table 6
Cigarettes/day	15	*IREB2*	rs17484524	G	2.01E-26	Web Table 6
Cigarettes/day	15	*IREB2*	rs2009746	G	1.52E-25	Web Table 6
Cigarettes/day	15	*IREB2*	rs17484235	G	1.14E-25	Web Table 6
Cigarettes/day	15	*LOC123688*	rs8034191	T	1.68E-31	Web Table 6
Cigarettes/day	15	*IREB2*	rs2568494	G	3.39E-24	Web Table 6
Cigarettes/day	15	*IREB2*	rs2656052	C	3.76E-24	Web Table 6
Cigarettes/day	15	*IREB2*	rs7181486	T	2.46E-24	Web Table 6
Cigarettes/day	15	*IREB2*	rs17483929	G	2.70E-24	Web Table 6
Cigarettes/day	15	*IREB2*	rs17483548	G	9.66E-24	Web Table 6
Cigarettes/day	15	*IREB2*	rs2656065	G	4.88E-25	Web Table 6
Cigarettes/day	15	*IREB2*	rs17483721	T	7.34E-24	Web Table 6
Cigarettes/day	15	*IREB2*	rs17405217	T	9.09E-24	Web Table 6
Cigarettes/day	15	*CHRNA3 CHRNB4*	rs1021070	G	2.16E-08	Web Table 6
Cigarettes/day	15	*CHRNA3 CHRNB4*	rs7181405	G	2.31E-08	Web Table 6
Cigarettes/day	15	*CHRNA5*	rs2036527	G	1.20E-32	Web Table 6
Cigarettes/day	15	*CHRNB4*	rs12905641	T	1.07E-07	Web Table 6
Cigarettes/day	15	*CHRNA5*	rs951266	G	3.00E-33	Web Table 6
Cigarettes/day	15	*CHRNB4*	rs8038920	G	6.98E-08	Web Table 6
Cigarettes/day	15	*ADAMTS7*	rs1994016	T	3.33E-10	Web Table 6
Cigarettes/day	15	*CHRNA5*	rs7180002	T	4.11E-33	Web Table 6
Cigarettes/day	15	*CHRNA5*	rs17486278	C	5.91E-33	Web Table 6
Cigarettes/day	15	*ADAMTS7*	rs3743057	T	9.45E-06	Web Table 6
Cigarettes/day	15	*ADAMTS7*	rs7177699	T	6.78E-11	Web Table 6
Cigarettes/day	15	*ADAMTS7*	rs3825807	G	1.29E-10	Web Table 6
Cigarettes/day	15	*ADAMTS7*	rs2277545	T	7.55E-11	Web Table 6
Cigarettes/day	15	*ADAMTS7*	rs12903203	T	1.08E-10	Web Table 6
Cigarettes/day	15	*ADAMTS7 MORF4L1*	rs7178051	T	1.07E-05	Web Table 6
Cigarettes/day	15	*ADAMTS7*	rs1564499	T	4.70E-06	Web Table 6
Cigarettes/day	15	*CHRNA3*	rs1317286	G	5.26E-33	Web Table 6

Cigarettes/day	15	*ADAMTS7*	rs2904228	G	5.99E-06	Web Table 6
Cigarettes/day	15	*ADAMTS7*	rs12905740	T	3.08E-06	Web Table 6
Cigarettes/day	15	*ADAMTS7*	rs1994017	T	2.86E-06	Web Table 6
Cigarettes/day	15	*ADAMTS7*	rs4380028	T	8.92E-06	Web Table 6
Cigarettes/day	15	*ADAMTS7 MORF4L1*	rs6495335	T	8.70E-06	Web Table 6
Cigarettes/day	15	*ADAMTS7 MORF4L1*	rs7176187	T	5.13E-06	Web Table 6
Cigarettes/day	15	*IREB2*	rs1394371	T	2.36E-18	Web Table 6
Cigarettes/day	15	*CHRNB4*	rs17487223	T	4.23E-29	Web Table 6
Cigarettes/day	15	*ADAMTS7*	rs1383636	G	1.24E-06	Web Table 6
Cigarettes/day	15	*ADAMTS7*	rs922693	G	8.09E-07	Web Table 6
Cigarettes/day	15	*ADAMTS7*	rs8038189	G	6.75E-07	Web Table 6

SNP, single nucleotide polymorphism; GWAS, genome-wide association study; Chr, chromosome; *CHRNA5*, cholinergic receptor, nicotinic alpha 5; *C1orf100*, chromosome 1 open reading frame 100; *CHRNA3*, cholinergic receptor, nicotinic alpha 3; *LOC503519*, uncharacterized LOC503519; *PSMA4*, proteasome subunit alpha 4; *SPOCK2*, SPARC/osteonectin, cwcv and kazal like domains proteoglycan 2; *BDNFOS*, brain-derived neurotrophic factor opposite strand; *BDNF*, brain-derived neurotrophic factor; *PSMA4*, proteasome subunit alpha 4; *AGPHD1*, also known as *HYKK*, hydroxylysine kinase; *DBH*, dopamine beta-hydroxylase; *LOC100188947*, uncharacterized LOC100188947; *EGLN2*, egl-9 family hypoxia inducible factor 2; *LOC123688*, uncharacterized LOC123688; *IREB2*, iron responsive element binding protein 2; *CHRNB4*, cholinergic receptor, nicotinic beta 4; *ADAMTS7*, ADAM metallopeptidase with thrombospondin type 1 motif 7; *MORF4L1*, mortality factor 4 like 1.

Web Appendix 1

Step 1 MR Assumption Checking

The previously identified GWAS SNPs of cigarette smoking were tested for the three assumptions of the MR approach in GENOA: 1) SNPs are associated with the smoking variables; 2) the SNP affects the DNA methylation only through cigarette smoking (i.e., there is no direct effect from the SNP to the DNA methylation); and 3) the SNP does not share common causes with the DNA methylation (1).

Assumption 1. To test the first assumption, smoking variables were regressed on the instrument SNPs using logistic (for current smoking status or ever smoking status) mixed effects models, adjusting for age, sex, four PCs from the genotype data, five cell proportions, plate (technical batch), and random intercepts for family. The allele dosage from imputation was used for SNPs assuming an additive inheritance model.

Assumption 2. To test the second assumption, DNA methylation levels were regressed on an instrument SNP using linear mixed effect models adjusting for one of the two smoking variables, age, sex, four PCs from the genotype data, five cell proportions, plate, and random intercepts for family. This tests whether there is any effect of an instrument SNP on the DNA methylation that is not due to cigarette smoking.

In addition, we indirectly tested for exclusion restriction by investigating associations between an instrument SNP and measured current smoking-methylation confounders such as age and sex (2).

There can be a pathway from an instrument SNP to past smoking, which would have its own effect on the outcome. To test this, we created a new variable for past smoking (former

smoker) and checked its association with the instrument SNPs for current smoking. We used a *P*-value criterion of 0.05.

Assumption 3. SNP associations can be confounded by factors such as population stratification. We have adjusted for SNP PCs to reduce the confounding effect from population stratification; however, there can still be residual confounding or other unmeasured confounders.

Step 1 MR

We used a 2-stage least-squares (2SLS) regression for our analyses. To obtain unbiased estimates for 2-stage least-squares regression, the exogenous variables (covariates) were included in both first-stage and the second-stage regressions. First, each smoking variable was regressed on the instrument SNP S using logistic (for current smoking status or ever smoking status) mixed effects models, adjusting for age, sex, four PCs, five cell proportions, plate, and random intercepts for family (equation 1).

$$Smoking_{ij} = \beta_0 + \beta_1 * SNP\ S_{ij} + \beta_2 * age_{ij} + \beta_3 * sex_{ij} + \beta_4 * PC1_{ij} + \beta_5 * PC2_{ij} + \beta_6 * PC3_{ij} + \beta_7 * PC4_{ij} + \beta_8 * CD8T_{ij} + \beta_9 * CD4T_{ij} + \beta_{10} * NK_{ij} + \beta_{11} * Bcell_{ij} + \beta_{12} * Mono_{ij} + \beta_{13-24} * Plate1-12_{ij} + u_j + \varepsilon_{ijk}, \quad \text{(equation 1)}$$

where $Smoking_{ij}$ is the outcome variable for an individual *i* in family *j* with a logistic link function for binary outcomes (current smoking status or ever smoking status), u_j is a random intercept for family *j*, and ε_{ij} is a random error for an individual *i* in family *j*.

Second, DNA methylation levels were regressed on the predicted values of smoking obtained from equation 1 adjusting for age, sex, four PCs, five cell proportions, plate and random intercepts for family (equation 2).

$$DNA\ methylation\ levels_{ij} = \beta_0 + \beta_1 * \widehat{smoking}_{ij} + \beta_2 * age_{ij} + \beta_3 * sex_{ij} + \beta_4 * PC1_{ij} + \beta_5 * PC2_{ij} + \beta_6 * PC3_{ij} + \beta_7 * PC4_{ij} + \beta_8 * CD8T_{ij} + \beta_9 * CD4T_{ij} + \beta_{10} * NK_{ij} + \beta_{11} * Bcell_{ij} + \beta_{12} * Mono_{ij} + \beta_{13-24} * Plate1 - 12_{ij} + u_j + \varepsilon_{ij}, \quad \text{(equation 2)}$$

where $\widehat{smoking}_{ij}$ is the predicted value (from equation 1) for an individual *i* in family *j*, u_j is a random intercept for family *j*, and ε_{ij} is a random error for an individual *i* in family *j*.

In addition to a single SNP MR, we used a genetic risk score (GRS) as an instrument (3). We constructed GRSs for each smoking variable using SNPs that satisfy the MR assumptions and are not in high LD ($r^2 < 0.3$). When the coded allele was negatively associated with a smoking variable, we coded for the other allele by subtracting the allele dosage from 2.

Step 2 MR Assumption Checking

The candidate instrument SNPs of each of the CpGs were tested for the three assumptions of the MR approach: 1) SNPs are associated with the DNA methylation; 2) the SNP affects the inflammatory markers only through the DNA methylation (i.e. there is no direct effect of the SNP on the inflammatory marker levels); and 3) the SNP does not share common causes with the inflammatory markers.

Assumption 1. To test the first assumption, the DNA methylation levels were regressed on the SNPs using linear mixed effects models adjusting for age, sex, four PCs from genotype information, five cell proportions, plate (technical batch), and random intercepts for family. The allele dosage from imputation was used for SNPs assuming an additive inheritance model.

Assumption 2. To test the second assumption, inflammatory marker levels were regressed on an instrument SNP using linear mixed effect models adjusting for DNA methylation levels, age,

sex, four PCs from genotype information, five cell proportions, plate, and random intercepts for family. This regression analysis tests the direct effect of an instrument SNP on the inflammatory markers that is not due to the DNA methylation levels.

In addition, we indirectly tested for exclusion restriction by investigating associations between an instrument SNP and measured methylation-inflammation confounders such as age, sex, SNP PCs, and cell proportions (2). We used a p-value criterion of 0.05.

Assumption 3. SNP associations can be confounded by factors such as population stratification. We have adjusted for SNP PCs to reduce the confounding effect from population stratification; however, there can still be residual confounding or other unmeasured confounders.

Step 2 MR

First, DNA methylation levels were regressed on the instrument SNP using linear mixed effects models adjusting for age, sex, four PCs from genotype information, five cell proportions, plate, and random intercepts for family (equation 3).

$$DNA\ methylation\ levels_{ij} = \beta_0 + \beta_1 * SNP_{ij} + \beta_2 * age_{ij} + \beta_3 * sex_{ij} + \beta_4 * PC1_{ij} + \beta_5 * PC2_{ij} + \beta_6 * PC3_{ij} + \beta_7 * PC4_{ij} + \beta_8 * CD8T_{ij} + \beta_9 * CD4T_{ij} + \beta_{10} * NK_{ij} + \beta_{11} * Bcell_{ij} + \beta_{12} * Mono_{ij} + \beta_{13-24} * Plate1-12_{ij} + u_j + \varepsilon_{ijk}, \quad \text{(equation 3)}$$

where u_j is a random intercept for family j, and ε_{ijk} is a random error for an individual i in family j.

Second, inflammatory marker levels were regressed on the predicted values of DNA methylation levels from equation 3 adjusting for age, sex, four PCs, five cell proportions, plate, and random intercepts for family (equation 4).

$$Inflammatory\ marker\ levels_{ij}$$

$$= \beta_0 + \beta_1 * \widehat{methylation}_{ij} + \beta_2 * age_{ij} + \beta_3 * sex_{ij} + \beta_4 * PC1_{ij} + \beta_5 * PC2_{ij}$$

$$+ \beta_6 * PC3_{ij} + \beta_7 * PC4_{ij} + \beta_8 * CD8T_{ij} + \beta_9 * CD4T_{ij} + \beta_{10} * NK_{ij} + \beta_{11}$$

$$* Bcell_{ij} + \beta_{12} * Mono_{ij} + \beta_{13-24} * Plate1 - 12_{ij} + u_j + \varepsilon_{ijk}, \quad \text{(equation 4)}$$

where $Inflammatory\ marker\ levels_{ijk}$ are serum log(CRP), log(IL-6), log(IL-18), and fibrinogen levels of an individual *i* in family *j*. $\widehat{methylation}_{ij}$ is the predicted value from (equation 3) for an individual *i* in family *j*, u_j is a random intercept for family *j*, and ε_{ijk} is a random error for an individual *i* in family *j*.

In addition to a single SNP MR, we used a GRS as an instrument (3). We calculated pairwise LD between each pair of the instrument SNPs for cg03636183. Starting from the SNP with the highest F-value, we compared each SNP with the other SNPs and removed the other SNP if the two SNPs were in LD ($r^2 > 0.3$). When the coded allele was negatively associated with DNA methylation levels, we coded for the other allele by subtracting the allele dosage from 2 for construction of the GRS.

To demonstrate the independence of the step 1 and step 2 instrument SNPs, we checked r^2 between each pair of the instrument SNPs for current smoking and the instrument SNPs for cg03636183 in *F2RL3*.

In a mediation analysis, the associations between instruments and the instrumented exposures and outcomes can be checked to see if independences are violated (4). We have checked the association between the step 1 instrument SNPs for current smoking and the DNA methylation levels of cg03636183 adjusting for age, sex, four principal components, five cell proportions, plate, and random intercepts for family (4). We also checked the association between the step 2 instrument SNPs for cg03636183 and current smoking status adjusting for

age, sex, four principal components and random intercepts for family. In addition, we have checked the associations between potential instruments (both step 1 and step 2 instruments) and log(IL-18) levels adjusting for age, sex, four principal components, five cell proportions, plate, and random intercepts for family.

To estimate the indirect effect of current smoking on IL-18 levels through DNA methylation levels of a CpG site, an additional assumption on homogeneity of effect in the study population is necessary (2, 5). Non-parametric Balke-Pearl bounds is known to be informative for homogeneity of effect for binary or categorical instrument, binary exposure and outcome (6). In our analysis, the outcome (DNA methylation levels) in step 1 is a continuous variable; and the exposure (DNA methylation levels) and the outcome (inflammatory marker levels) in step 2 are continuous variable. Hence, we were not able to provide the non-parametric Balke-Pearl effect bounds. Instead, to investigate whether the effect of genetically "set" smoking amongst "compliers" operate similarly across the population under study to allow for a point identification of effects, we classified subjects into compliers and non-compliers groups and compared their characteristics. Here "compliers" are defined as subjects who would be a current smoker had they have a risk allele for cigarette smoking (genetically set to smoke), but would be a never or former smoker had they do not have a risk allele for cigarette smoking.

Web Appendix 2

Evaluation of the Assumptions in Step 1

We started with 210 SNPs that have been identified in the three previous GWAS of cigarette smoking in studies of African Americans or multi-ethnic studies (the full list of the 210 SNPs is available in **Web Table 1**) (7-9). Of the 210 SNPs evaluated for assumption 1 (i.e., SNPs associated with the smoking variables), we found significant associations with a total of 30 SNPs: 19 SNPs with current smoking status, and 11 SNPs with ever smoking status with a p-value criterion of 0.05 (**Web Table 3**). We did not apply multiple testing corrections because the SNPs were identified in previous GWAS studies and most of the SNPs were located in the 15q24-25 region. Most of the SNPs, 27 out of 30, were located in chromosome 15q24-25 region. Genes in the 15q24-25 region include nicotinic cholinergic receptor alpha3, alpha5, and beta4 genes (*CHRNA3*, *CHRNA5*, and *CHRNB4*), which have been associated with onset of smoking (10), serum cotinine level (11), nicotine dependency (12), nicotine addiction (13), and smoking cessation success (14). These 30 SNPs that satisfy assumption 1 were further investigated for assumption 2. We found SNPs with a significant effect on the DNA methylation levels after adjusting for smoking variables (p-value criterion of 0.05) and thus were excluded. The SNPs that did not satisfy assumption 2 for each of CpG markers were marked as "—" in **Tables 2-4** and **Web Tables 5-7**. We also estimated associations between the SNP and measured cigarette smoking-DNA methylation confounders such as age and sex. None of the SNPs were associated with age; however, five SNPs were associated with sex: rs4887069 (P = 0.03), rs6495308 (P = 0.03), rs7177514 (P = 0.03), rs8042059 (P = 0.03), and rs8042374 (P = 0.03). Since these 5 SNPs may not satisfy the exclusion restriction assumption, we have excluded those SNPs. Finally, a total of 25 instrument SNPs were available for smoking variables: 14 SNPs with

current smoking status, and 11 SNPs with ever smoking status. We have investigated the exclusion restriction assumption in several ways, however, the exclusion restriction assumption cannot be exhaustively tested empirically and must be justified conceptually. Hence, the assumption might not be satisfied.

For step 1 MR, we constructed a GRS which is composed of five SNPs out of the 14 SNPs for current smoking status that are not in high LD ($r^2 < 0.3$): GRS = [rs4074134 + (2 − rs1964678) + (2 − rs952216) + (2 − rs12915366) + (2 − rs1317286)]/5. When the coded allele was negatively associated with current smoking status, we coded for the other allele by subtracting the allele dosage from 2. The GRS was strongly associated with current smoking status ($\beta = 1.69$, SE = 0.43, $P = 8.7 \times 10^{-5}$, F-value = 15.78).

For step 1 MR, we also constructed a GRS for ever-smoking status which is composed of three SNPs out of the 11 SNPs that are not in high LD ($r^2 < 0.3$): GRS = [rs9920506 + rs4887077 + rs12286]/3. The GRS was strongly associated with ever smoking status ($\beta = 0.82$, SE = 0.26, $P = 0.002$, F-value = 9.65).

There can be a pathway from an instrument SNP to past smoking, which would have its own effect on the outcome. To test this, we created a new variable for past smoking and checked its association with the instrument SNPs for current smoking. None of the instrument SNPs for current smoking were associated with past smoking ($P > 0.05$). This may be due to differential nicotine-dependency between current and former smokers. If genes influence cigarette smoking, those genes may be more influential in stopping smoking (i.e., genetically afflicted smokers find it harder to stop smoking because of intense nicotine addiction, but non-afflicted smokers may be able to stop smoking more easily). If this is true, then former smokers are less likely to be afflicted smokers, but current smokers are more likely to be afflicted ones. Therefore, we can

expect different genotype frequencies in nicotine-related genes between current smokers and never smokers, but no difference between former smokers and never smokers. **Web Table 11** presents the distributions of instrument SNPs by smoking status (current, former, and never). The genotype distributions were significantly different between current vs. never (eg. χ^2 P-value for rs4074134 = 0.02); but no there was difference between former vs. never (e.g., χ^2 P-value for rs4074134 = 0.4). This finding supports that it is less likely that there is a path from instrument SNPs for current smoking to the outcome through past (former) smoking.

Evaluation of the Assumptions in Step 2

In step 2, we extended our step 1 approach to investigate the effects of DNA methylation level changes, which are induced by cigarette smoking, on inflammatory markers. Candidates for step 2 instrument SNPs were identified by reviewing literatures on mQTL studies and investigating cis-mQTLs within 10kb from the genes where the CpG sites were located. To avoid false positives, we only investigated genetic variants with minor allele frequency ≥ 0.05.

Out of 64 common genetic variants within 10kb from the *F2RL3* gene, 20 genetic variants were strong cis-mQTLs for cg03636183 with Bonferroni corrected criterion ($0.05/64 = 7.81 \times 10^{-4}$) (**Web Table 6**). We compared our cis-mQTLs to the mQTL results from the previous study of 77 HapMap Yoruba samples (15). The top cis-mQTL SNP (rs2227341 with a $P = 1.3 \times 10^{-66}$ in GENOA) for cg03636183 in the *F2RL3* gene had also been found in the HapMap Yoruba samples ($P = 9.75 \times 10^{-6}$) (http://eqtl.uchicago.edu/Methylation/cis-meQTL.results). Another cis-mQTL, rs773904 ($P = 2.8 \times 10^{-10}$ in GENOA), was found in the mQTL study of lymphoblastoid cells ($P = 4.96 \times 10^{-8}$) and T-cells ($P = 3.08 \times 10^{-8}$) from the umbilical cords of 111 newborns (the GenCord cohort) (http://dx.doi.org/10.7554/eLife.00523.012) (16). The 20 identified genetic variants were further

checked for the direct effect on the inflammatory markers (assumption 2), and three SNPs for log(IL-6), and fibrinogen were excluded with a p-value criterion of 0.05. In addition, we estimated associations between the SNP and measured DNA methylation-IL18 confounders. We have tested for age, sex, four SNP PCs, and cell proportions. Two SNPs including rs2227370 (P = 0.01) and rs2227371 (P = 0.01) were significantly associated with age. However, none of the 20 instrument SNPs for cg03636183 were associated with sex. Two SNPs including rs773903 (P = 0.02) and rs773904 (P = 0.02) were significantly associated with SNP PC1; rs56298289 (P = 0.05) was significantly associated with SNP PC2; rs2227359 (P = 0.04) and rs57708423 (P = 0.04) were significantly associated with SNP PC3; none of the SNPs were associated with SNP PC4. rs57708423 (P = 0.03) and rs57816869 (0.002) were significantly associated with monocytes; the other cell proportions were not associated with any of the SNPs. In total, 8 SNPs were significantly associated with measured exposure-outcome confounders, we have excluded those SNPs. Finally, there were 12 instrument SNPs for the DNA methylation levels of cg03636183. We have investigated the exclusion restriction assumption in several ways, however, the exclusion restriction assumption cannot be exhaustively tested empirically and must be justified conceptually. Hence, the assumption might not be satisfied.

For step 2 MR, we calculated pairwise LD between each pair of the 12 instrument SNPs for cg03636183. Starting from the SNP with the highest F-value, we compared each SNP with the other SNPs and removed the other SNP if the two SNPs were in high LD ($r^2 > 0.3$). There were 5 SNPs left and the GRS for cg03636183 was calculated as follows: GRS = [(2 − rs2227341) + (2 − rs10418195) + (2 − rs773895) + rs7245967 + (2 − rs2981474)]/5. The GRS was significantly associated with the DNA methylation levels of cg03636183 (β = 1.41, SE = 0.10, P = 1.6E-35, F-value = 197).

We did not find any cis-mQTLs for cg19859270 in the *GPR15* gene (excluded from the step 2 MR analyses).

To check the independence of the step 1 and step 2 instrument SNPs, we calculated r^2 between each pair of the instrument SNPs for current smoking and the instrument SNPs for cg03636183 in *F2RL3*. The largest r^2 between the step 1 instrument SNPs and the step 2 instrument SNPs was 0.02. These results support that the two sets of SNPs are independent.

We also have checked associations between potential instruments and the instrumented exposures and outcomes. None of the step 1 instrument SNPs for current smoking were significantly associated with cg03636183. We also checked the association between the step 2 instrument SNPs for cg03636183 and current smoking status; none of the SNPs were significantly associated with current smoking status (**Web Table 9**).

To investigate homogeneity of the estimated effect, we estimated the proportion of compliers assuming 1 or 2 copies of rs4074134 coded allele is "treated". The proportion of compliers was (509 + 43)/822 = 0.67. We compared compliers (N = 552) to non-compliers (N = 270) in terms of several covariates. The compliers and non-compliers were not substantially different in terms of age, sex, BMI, log(CRP), log(IL-6), and log(IL-18) levels. However, compliers had lower fibrinogen levels compared to non-compliers (364.18 ± 77.09 mg/dL for compliers and 379.62 ± 86.63 mg/dL for non-compliers, p-value for the difference = 0.02) (**Web Table 10**).

We also investigated the MR association between the GRS for current smoking status and IL-18 levels across strata of a step 2 instrument, rs2227341 (0 coded allele vs 1 or 2 coded allele). There were 537 sample with 0 coded allele for rs2227341 and 285 samples with 1 or 2 coded alleles for rs2227341. In both strata, the GRS was significantly associated with the current

smoking status (P = 0.006 and 0.025 for 0 vs 1-2 coded allele strata, respectively). Using the GRS as an instrument, the MR-estimates for the association between current smoking and IL-18 level were 0.03 and 0.069, respectively. From the limited sample size and power in the stratified analyses, the MR-estimates were not significant (P = 0.96 and 0.31). However, the estimates can be interpreted as 0.3% ($=e^{0.003}$) and 7% ($=e^{0.069}$) increases in IL-18 levels with current smoking status. These substantially differing results support our findings.

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Web Table 2. Associations between smoking variables (current smoking status and ever smoking status), and inflammatory markers (CRP, IL-6, IL-18, and fibrinogen) adjusting for age and sex in GENOA Phase II (Jackson, Mississippi; 2000–2005)

Smoking Variable	Inflammatory Marker	*N*	β	SE	*P*
Current smoking status	log(CRP)	820	0.2378	0.1133	0.0366
	log(IL-6)	717	0.1758	0.0635	0.0059
	log(IL-18)	712	0.1154	0.0684	0.0924
	Fibrinogen	797	28.8445	8.6349	0.0009
Ever smoking status	log(CRP)	820	0.1802	0.0800	0.0249
	log(IL-6)	717	0.1115	0.0462	0.0162
	log(IL-18)	712	0.0789	0.0489	0.1074
	Fibrinogen	797	5.4107	6.0792	0.3741

CRP, C-reactive protein; IL-6, interleukin-6; IL-18, interleukin-18; GENOA, Genetic Epidemiology Network of Arteriopathy; SE, standard error.

Web Table 3. SNPs that are significantly associated with current smoking status (19 SNPs) and ever smoking status (11 SNPs) in GENOA (Jackson, Mississippi; 2000–2005) out of the 210 previous smoking GWAS SNPs

Smoking Variable	Gene	Region	Location (Build 37)	SNP	LD (r^2)	CAF	β	SE	*P*	*F*-Value
Current smoker (*N* = 822)	*BDNF-AS*	Intron	11:27647285	rs4074134	1	0.17	0.40	0.20	0.04	4.07
	BDNF-AS	Intron	11:27648580	rs4923457	0.99998	0.17	0.40	0.20	0.04	4.07
	BDNF-AS	Intron	11:27656789	rs4923460	0.96	0.17	0.40	0.20	0.04	4.15
	IREB2	Intron	15:78754000	rs1964678	2.2E-04	0.28	-0.46	0.20	0.02	5.52
	HYKK	Intron	15:78819202	rs952216	9.4E-06	0.13	-0.63	0.28	0.02	5.06
	HYKK	Intron	15:78821606	rs11636131	1.4E-06	0.14	-0.59	0.27	0.03	4.58
	HYKK	Intron	15:78821914	rs11632604	1.8E-06	0.14	-0.59	0.27	0.03	4.58
	HYKK	Intron	15:78822065	rs12910289	7.3E-06	0.14	-0.58	0.27	0.04	4.49
	HYKK	Intron	15:78824235	rs1504546	3.2E-06	0.14	-0.59	0.27	0.03	4.62
	HYKK	Intron	15:78826912	rs12916999	3.9E-06	0.14	-0.59	0.27	0.03	4.62
	PSMA4	Upstream 2KB	15:78831753	rs12915366	4.6E-06	0.14	-0.59	0.27	0.03	4.62
	PSMA4	Upstream 2KB	15:78832397	rs12916483	5.0E-06	0.14	-0.59	0.27	0.03	4.67
	PSMA4	UTR 5 prime	15:78832792	rs3813571	2.2E-06	0.14	-0.60	0.27	0.03	4.75
	CHRNA3	Intron	15:78896129	rs1317286	1.9E-03	0.27	0.36	0.18	0.04	4.12
	CHRNA3	Intron	15:78907406	rs7177514	4.6E-04	0.29	-0.40	0.18	0.03	4.67
	CHRNA3	Intron	15:78907656	rs6495308	3.2E-04	0.29	-0.39	0.18	0.04	4.45
	CHRNA3	Intron	15:78907859	rs8042059	4.6E-04	0.29	-0.40	0.18	0.03	4.71
	CHRNA3	Intron	15:78908032	rs8042374	4.4E-04	0.29	-0.40	0.18	0.03	4.67
	CHRNA3	Intron	15:78909070	rs4887069	5.5E-04	0.30	-0.39	0.19	0.04	4.41
				GRS[a]			1.69	0.43	8.7E-5	15.78
Ever smoker (*N* = 822)	*CHRNB4*	Intron	15:78931057	rs9920506	1	0.76	0.30	0.15	0.05	3.88
	CHRNB4	Intron	15:78945040	rs8023822	0.53	0.79	0.40	0.15	0.01	6.55
	LOC105370913	Upstream 7KB	15:78978364	rs4887077	0.01	0.08	0.48	0.22	0.03	4.67
	LOC105370913	Upstream 2KB	15:78983559	rs11638372	0.01	0.07	0.47	0.22	0.04	4.45
	LOC105370913	Upstream 1KB	15:78984214	rs922692	0.01	0.07	0.49	0.24	0.04	4.24

LOC105370913	Intron	15:78997076	rs11072791	0.01	0.08	0.49	0.22	0.03	4.97
ADAMTS7	Downstream 500B	15:79051759	rs12286	0.01	0.09	0.56	0.21	0.01	7.24
ADAMTS7	Intron	15:79056769	rs1809420	0.02	0.09	0.60	0.19	0.00	9.92
ADAMTS7	Intron	15:79064667	rs7174367	0.02	0.09	0.61	0.20	0.00	9.24
ADAMTS7	Missense	15:79089111	rs3825807	0.03	0.14	0.45	0.18	0.01	6.55
ADAMTS7	Intron	15:79089734	rs7177699	0.03	0.13	0.43	0.18	0.02	5.90
			GRS[b]			0.82	0.26	0.002	9.65

SNP, single nucleotide polymorphism; GENOA, Genetic Epidemiology Network of Arteriopathy; GWAS, genome-wide association study; LD, linkage disequilibrium; CAF, coded allele frequency; SE, standard error; *BDNF-AS*, brain-derived neurotrophic factor antisense RNA; *IREB2*, iron responsive element binding protein 2; *HYKK*, hydroxylysine kinase; *PSMA4*, proteasome subunit alpha 4; *CHRNA3*, cholinergic receptor, nicotinic alpha 3; GRS, genetic risk score; *CHRNB4*, cholinergic receptor, nicotinic beta 4; *LOC105370913*, uncharacterized LOC105370913; *ADAMTS7*, ADAM metallopeptidase with thrombospondin type 1 motif 7.

All models were adjusted for age, sex, four principal components, and random intercepts for family.

[a] GRS = [rs4074134 + (2 − rs1964678) + (2 − rs952216) + (2 − rs12915366) + (2 − rs1317286)]/5. When the coded allele was negatively associated with current smoking status, we coded for the other allele by subtracting the allele dosage from 2.

[b] GRS = [rs9920506 + rs4887077 + rs12286]/3.

Web Table 4. Step 1 Mendelian randomization results between current smoking status and the DNA methylation levels of cg13668129 in *HNRPUL1*, cg01500140 in *LIM2*, and cg11314684 in *AKT3* (GENOA; Jackson, Mississippi; 2000–2005)

Gene	SNP [a]	cg13668129			cg01500140			cg11314684		
		β [b]	SE	*P*	β [b]	SE	*P*	β [b]	SE	*P*
BDNF-AS	rs4074134	−0.04	0.02	0.06	0.01	0.03	0.71	−0.01	0.03	0.86
BDNF-AS	rs4923457	−0.04	0.02	0.06	0.01	0.03	0.71	−0.01	0.03	0.86
BDNF-AS	rs4923460	−0.04	0.02	0.09	0.01	0.03	0.82	0.0005	0.03	0.99
IREB2	rs1964678	−0.04	0.02	0.10	0.01	0.03	0.72	−0.01	0.03	0.85
HYKK	rs952216	−0.02	0.02	0.25	0.04	0.03	0.18	−0.02	0.03	0.55
HYKK	rs11636131	−0.03	0.02	0.23	0.04	0.03	0.18	−0.02	0.03	0.56
HYKK	rs11632604	−0.03	0.02	0.24	0.04	0.03	0.18	−0.02	0.03	0.56
HYKK	rs12910289	−0.03	0.02	0.23	0.04	0.03	0.18	−0.02	0.03	0.53
HYKK	rs1504546	−0.03	0.02	0.24	0.04	0.03	0.18	−0.02	0.03	0.56
HYKK	rs12916999	−0.03	0.02	0.24	0.04	0.03	0.18	−0.02	0.03	0.56
PSMA4	rs12915366	−0.03	0.02	0.24	0.04	0.03	0.18	−0.02	0.03	0.56
PSMA4	rs12916483	−0.03	0.02	0.24	0.04	0.03	0.18	−0.02	0.03	0.56
PSMA4	rs3813571	−0.03	0.02	0.24	0.04	0.03	0.18	−0.02	0.03	0.60
CHRNA3	rs1317286	−0.05	0.03	0.03	0.06	0.03	0.07	−0.03	0.04	0.44
	GRS [c]	−0.02	0.01	0.18	0.01	0.02	0.56	−0.01	0.02	0.68

DNA, deoxyribonucleic acid; *HNRPUL1*, heterogeneous nuclear ribonucleoprotein U like 1; *LIM2*, lens intrinsic membrane protein 2; *AKT3*, AKT serine/threonine kinase 3; GENOA, Genetic Epidemiology Network of Arteriopathy; *BDNF-AS*, brain-derived neurotrophic factor antisense RNA; *IREB2*, iron responsive element binding protein 2; *HYKK*, hydroxylysine kinase; *PSMA4*, proteasome subunit alpha 4; *CHRNA3*, cholinergic receptor, nicotinic alpha 3; GRS, genetic risk score.

[a] The instrument SNPs were identified in previous GWAS of cigarette smoking in an independent cohort and satisfied the assumptions of MR in GENOA.

[b] We described a beta coefficient of an exposure (current smoking status) in the second stage of 2-stage least squares regressions as "β". All models were adjusted for age, sex, four principal components, five cell proportions, plate, and random intercepts for family. "—" stands for "missing on the MR results" because of the violation of assumption 2.

[c] GRS = [rs4074134 + (2 − rs1964678) + (2 − rs952216) + (2 − rs12915366) + (2 − rs1317286)]/5. When the coded allele was negatively associated with current smoking status, we coded for the other allele by subtracting the allele dosage from 2.

Web Table 5. SNPs that are significantly associated with the DNA methylation levels of cg03636183 in the *F2RL3* gene in GENOA (Jackson, Mississippi; 2000–2005)

CpG	SNP	Coded Allele Frequency	β [a]	SE	*P*	*F*-Value
cg03636183	rs2227341 [b]	0.19	−1.14	0.05	1.3E-66	480
	rs2227353	0.20	−1.06	0.05	3.0E-62	432
	rs2227359	0.11	−1.06	0.07	1.2E-36	205
	rs56298289	0.22	−0.73	0.06	5.3E-31	165
	rs2227368	0.08	−1.02	0.09	1.8E-24	123
	rs10418195	0.08	−0.89	0.09	7.2E-20	95
	rs57708423	0.19	−0.59	0.06	1.2E-19	93
	rs57816869	0.26	−0.42	0.05	2.2E-13	59
	rs773904 [b]	0.65	−0.33	0.05	2.8E-10	42
	rs773903	0.65	−0.33	0.05	2.8E-10	42
	rs2227370	0.22	0.35	0.06	1.4E-09	39
	rs2227371	0.23	0.34	0.06	1.8E-09	38
	rs773905	0.78	−0.25	0.06	1.4E-05	19
	rs773895	0.78	−0.24	0.06	4.1E-05	17
	rs773899	0.79	−0.23	0.06	5.6E-05	16
	rs1044773	0.79	−0.23	0.06	6.4E-05	16
	rs773901	0.75	−0.22	0.05	6.90E-05	16
	rs7245967	0.19	0.24	0.06	1.60E-04	15
	rs2981474	0.38	−0.20	0.06	3.7E-04	13
	rs2608732	0.75	−0.19	0.05	6.3E-04	12
	GRS [c]		1.41	0.10	1.6E-35	197

SNP, single nucleotide polymorphism; DNA, deoxyribonucleic acid; *F2RL3*, coagulation factor II (thrombin) receptor-like 3; GENOA, Genetic Epidemiology Network of Arteriopathy; CpG, cytosine and guanine separated by one phosphate; SE, standard error; GRS, genetic risk score.

[a] We described a beta coefficient of a SNP as "β" from the regression of DNA methylation levels of cg03636183 on each SNP adjusting for age, sex, four principal components, five cell proportions, plate, and random intercepts for family (N = 822).

[b] SNPs found in an independent cohort and in GENOA.

[c] GRS (genetic risk score) = [(2 − rs2227341) + (2 − rs10418195) + (2 − rs773895) + rs7245967 + (2 − rs2981474)]/5. When the coded allele was negatively associated with the DNA methylation levels of cg03636183, we coded for the other allele by subtracting the allele dosage from 2.

Web Table 6. Step 1 Mendelian randomization results between current smoking status and the Beta-values of DNA methylation levels of cg03636183 in the *F2RL3* gene, and cg19859270 in the *GPR15* gene (GENOA; Jackson, Mississippi; 2000–2005)

Gene	SNP [a]	cg03636183			cg19859270		
		β [b]	SE	*P*	β [b]	SE	*P*
BDNF-AS	rs4074134	−0.05	0.01	4.5E-11	−0.010	0.002	1.5E-05
BDNF-AS	rs4923457	−0.06	0.01	4.6E-11	−0.010	0.002	1.5E-05
BDNF-AS	rs4923460	−0.05	0.01	4.6E-11	−0.010	0.002	2.2E-05
IREB2	rs1964678	−0.04	0.01	2.1E-08	−0.009	0.002	5.5E-06
HYKK	rs952216	−0.04	0.01	2.2E-08	−0.010	0.002	6.1E-07
HYKK	rs11636131	−0.04	0.01	2.6E-08	−0.011	0.002	5.9E-07
HYKK	rs11632604	−0.04	0.01	2.7E-08	−0.011	0.002	6.0E-07
HYKK	rs12910289	−0.04	0.01	2.7E-08	−0.011	0.002	5.3E-07
HYKK	rs1504546	−0.04	0.01	3.0E-08	−0.011	0.002	6.1E-07
HYKK	rs12916999	−0.04	0.01	3.1E-08	−0.011	0.002	6.1E-07
PSMA4	rs12915366	−0.04	0.01	3.2E-08	−0.011	0.002	6.2E-07
PSMA4	rs12916483	−0.04	0.01	3.3E-08	−0.011	0.002	6.2E-07
PSMA4	rs3813571	−0.04	0.01	5.9E-08	−0.010	0.002	7.3E-07
CHRNA3	rs1317286	—	—	—	−0.008	0.002	9.0E-04
	GRS [c]	−0.04	0.01	1.8E-07	−0.006	0.002	6.7E-03

DNA, deoxyribonucleic acid; *F2RL3*, coagulation factor II (thrombin) receptor-like 3; *GPR15*, G protein-coupled receptor 15; GENOA, Genetic Epidemiology Network of Arteriopathy; SNP, single nucleotide polymorphism; SE, standard error; *BDNF-AS*, brain-derived neurotrophic factor antisense RNA; *IREB2*, iron responsive element binding protein 2; *HYKK*, hydroxylysine kinase; *PSMA4*, proteasome subunit alpha 4; *CHRNA3*, cholinergic receptor, nicotinic alpha 3; GRS, genetic risk score.

[a] The instrument SNPs were identified in previous GWAS of cigarette smoking in an independent cohort and satisfied the assumptions of MR in GENOA.

[b] We described a beta coefficient of an exposure (current smoking status) in the second stage of 2-stage least squares regressions as "β". All models were adjusted for age, sex, four principal components, five cell proportions, plate, and random intercepts for family. "—" stands for "missing on the MR results" because of the violation of assumption 2.

[c] GRS = [rs4074134 + (2 − rs1964678) + (2 − rs952216) + (2 − rs12915366) + (2 − rs1317286)]/5. When the coded allele was negatively associated with current smoking status, we coded for the other allele by subtracting the allele dosage from 2.

Web Table 7. Step 1 Mendelian randomization results between ever smoking status and the beta-values of DNA methylation levels of cg03636183 in the *F2RL3* gene, and cg19859270 in the *GPR15* gene (GENOA; Jackson, Mississippi; 2000–2005)

Gene	SNP [a]	cg03636183			cg19859270		
		β [b]	SE	*P*	β [b]	SE	*P*
CHRNB4	rs9920506	−0.053	0.008	1.0E-09	−0.010	0.002	1.4E-05
CHRNB4	rs8023822	−0.049	0.008	1.1E-09	−0.008	0.002	1.4E-04
LOC105370913	rs4887077	−0.045	0.008	1.0E-07	−0.008	0.002	3.3E-04
LOC105370913	rs11638372	−0.046	0.008	5.5E-08	−0.008	0.002	2.6E-04
LOC105370913	rs922692	−0.047	0.008	2.8E-08	−0.008	0.002	2.4E-04
LOC105370913	rs11072791	−0.048	0.008	1.1E-08	−0.009	0.002	8.9E-05
ADAMTS7	rs12286	−0.040	0.008	2.4E-07	−0.008	0.002	1.3E-04
ADAMTS7	rs1809420	−0.035	0.007	1.9E-06	−0.007	0.002	2.8E-04
ADAMTS7	rs7174367	−0.038	0.007	2.8E-07	−0.007	0.002	1.9E-04
ADAMTS7	rs3825807	—	—	—	−0.008	0.002	7.3E-05
ADAMTS7	rs7177699	—	—	—	−0.009	0.002	8.8E-05
	GRS [c]	−0.036	0.007	8.0E-07	−0.007	0.002	3.9E-04

DNA, deoxyribonucleic acid; *F2RL3*, coagulation factor II (thrombin) receptor-like 3; *GPR15*, G protein-coupled receptor 15; GENOA, Genetic Epidemiology Network of Arteriopathy; SNP, single nucleotide polymorphism; CI, confidence interval; *CHRNB4*, cholinergic receptor, nicotinic beta 4; *LOC105370913*, uncharacterized LOC105370913; *ADAMTS7*, ADAM metallopeptidase with thrombospondin type 1 motif 7; GRS, genetic risk score.

[a] The instrument SNPs were identified in previous GWAS of cigarette smoking in an independent cohort and satisfied the assumptions of MR in GENOA.

[b] We described a beta coefficient of an exposure (ever smoking status) in the second stage of 2-stage least squares regressions as "β". All models were adjusted for age, sex, four principal components, five cell proportions, plate, and random intercepts for family.

"—" stands for "missing on the MR results" because of the violation of assumption 2.

[c] GRS = [rs9920506 + rs4887077 + rs12286]/3. When the coded allele was negatively associated with ever smoking status, we coded for the other allele by subtracting the allele dosage from 2.

Web Table 8. Step 2 Mendelian randomization results between the Beta-values of DNA methylation levels of cg03636183 in the *F2RL3* gene and inflammatory markers, log(CRP), log(IL6), log(IL18), and fibrinogen (GENOA; Jackson, Mississippi; 2000–2005)

Instrument	log(CRP)			log(IL6)			log(IL18)			Fibrinogen		
SNP [a]	β [b]	SE	*P*	β [b]	SE	*P*	β [b]	SE	*P*	β [b]	SE	*P*
rs2227341 [c]	0.57	0.81	0.48	−0.01	0.47	0.98	−1.36	0.50	6.3E-03	13.23	62.05	0.83
rs2227353	0.57	0.84	0.49	−0.06	0.49	0.90	−1.54	0.51	2.9E-03	32.39	63.79	0.61
rs2227368	0.18	1.09	0.87	0.17	0.63	0.79	−2.01	0.65	2.2E-03	−39.61	83.43	0.64
rs10418195	0.39	1.12	0.73	0.04	0.65	0.95	−2.16	0.67	1.4E-03	−17.39	85.65	0.84
rs773905	−0.48	1.27	0.71	−0.58	0.73	0.43	−2.47	0.74	1.0E-03	−120.50	96.41	0.21
rs773901	−0.52	1.28	0.68	−0.60	0.74	0.41	−2.60	0.75	5.9E-04	−133.95	96.92	0.17
rs773895	0.20	1.25	0.87	—	—	—	−2.29	0.73	2.0E-03	—	—	—
rs7245967	−0.57	1.29	0.66	−0.51	0.75	0.49	−2.34	0.76	2.2E-03	−135.03	98.25	0.17
rs773899	0.12	1.25	0.92	—	—	—	−2.25	0.73	2.5E-03	—	—	—
rs1044773	0.11	1.25	0.93	—	—	—	−2.25	0.74	2.4E-03	—	—	—
rs2981474	−0.42	1.28	0.74	−0.46	0.74	0.53	−2.51	0.75	8.6E-04	−138.22	97.16	0.16
rs2608732	−0.62	1.29	0.63	−0.62	0.74	0.41	−2.57	0.75	7.5E-04	−142.89	97.89	0.15
GRS [d]	0.57	0.81	0.48	−0.01	0.47	0.98	−1.36	0.50	6.3E-03	13.23	62.05	0.83

DNA, deoxyribonucleic acid; *F2RL3*, coagulation factor II (thrombin) receptor-like 3; CRP, C-reactive protein; IL-6, interleukin-6; IL-18, interleukin-18; GENOA, Genetic Epidemiology Network of Arteriopathy; SNP, single nucleotide polymorphism; SE, standard error.

[a] All the instrument SNPs were located within 10kb of the *F2RL3* gene and satisfied the assumptions of MR in GENOA.

[b] We described a beta coefficient of an exposure (cg03636183) in the second stage of 2-stage least squares regressions as "β". All models were adjusted for age, sex, four principal components, five cell proportions, plate, and random intercepts for family.

"—" stands for "missing on the MR results" because of the violation of assumption 2.

[c] A SNP identified as a methylation quantitative trait loci for cg03636183 in an independent cohort and in GENOA.

[d] GRS = [(2 − rs2227341) + (2 − rs10418195) + (2 − rs773895) + rs7245967 + (2 − rs2981474)]/5. When the coded allele was negatively associated with the DNA methylation levels of cg03636183, we coded for the other allele by subtracting the allele dosage from 2.

Web Table 9. Associations between steps 1 and 2 instruments and the instrumented exposures and outcomes (GENOA; Jackson, Mississippi; 2000–2005)

SNP	Current Smoking			cg03636183			log(IL-18)		
	β [a]	SE	*P*	β [b]	SE	*P*	β [b]	SE	*P*
Step 1 instrument									
rs4074134	0.40	0.20	0.04	−0.05	0.06	0.42	−0.02	0.04	0.57
rs4923457	0.40	0.20	0.04	−0.05	0.06	0.43	−0.02	0.04	0.57
rs4923460	0.40	0.20	0.04	−0.05	0.06	0.41	−0.02	0.04	0.59
rs1964678	−0.46	0.20	0.02	0.0003	0.05	1.00	−0.04	0.04	0.28
rs952216	−0.63	0.28	0.02	0.02	0.07	0.79	0.05	0.05	0.28
rs11636131	−0.59	0.27	0.03	−0.01	0.07	0.94	0.06	0.05	0.22
rs11632604	−0.59	0.27	0.03	−0.01	0.07	0.94	0.06	0.05	0.22
rs12910289	−0.58	0.27	0.04	−0.01	0.07	0.93	0.06	0.05	0.22
rs1504546	−0.59	0.27	0.03	−0.01	0.07	0.94	0.06	0.05	0.21
rs12916999	−0.59	0.27	0.03	−0.01	0.07	0.94	0.06	0.05	0.21
rs12915366	−0.59	0.27	0.03	−0.01	0.07	0.93	0.06	0.05	0.20
rs12916483	−0.59	0.27	0.03	−0.01	0.07	0.93	0.06	0.05	0.20
rs3813571	−0.60	0.27	0.03	−0.01	0.07	0.88	0.05	0.05	0.25
rs1317286	0.36	0.18	0.04	0.07	0.05	0.20	−0.02	0.04	0.62
GRS [c]	1.69	0.43	8.7E-05	−0.03	0.11	0.77	−0.001	0.08	0.99
Step 2 instrument									
rs2227341	0.04	0.23	0.85	−1.14	0.05	1.3E-66	0.10	0.05	0.04
rs2227353	0.09	0.22	0.68	−1.06	0.05	3.0E-62	0.11	0.04	0.02
rs2227368	−0.07	0.34	0.84	−1.02	0.09	1.8E-24	0.13	0.07	0.06
rs10418195	−0.09	0.32	0.78	−0.89	0.09	7.2E-20	0.13	0.07	0.06
rs773905	−0.10	0.19	0.59	−0.25	0.06	1.4E-05	0.03	0.04	0.41
rs773901	−0.33	0.18	0.07	−0.22	0.05	6.9E-05	0.05	0.04	0.20
rs773895	0.15	0.20	0.46	−0.24	0.06	4.1E-05	0.03	0.04	0.41

rs7245967	0.003	0.21	0.99	0.24	0.06	1.6E-04	-0.03	0.04	0.53
rs773899	0.20	0.20	0.32	−0.23	0.06	5.6E-05	0.03	0.04	0.53
rs1044773	0.20	0.20	0.31	−0.23	0.06	6.4E-05	0.03	0.04	0.53
rs2981474	−0.32	0.20	0.12	−0.20	0.06	3.7E-04	0.05	0.04	0.23
rs2608732	−0.30	0.18	0.10	−0.19	0.05	6.3E-04	0.04	0.04	0.34
GRS [d]	0.13	0.39	0.73	1.41	0.10	1.6E-35	−0.17	0.08	0.03

GENOA, Genetic Epidemiology Network of Arteriopathy; SNP, single nucleotide polymorphism; SE, standard error.

[a] The beta coefficient of a SNP or a GRS adjusting for age, sex, four principal components, and random intercepts for family.

[b] The beta coefficient of a SNP or a GRS adjusting for age, sex, four principal components, five cell proportions, plate, and random intercepts for family.

[c] GRS (genetic risk score) = [rs4074134 + (2 − rs1964678) + (2 − rs952216) + (2 − rs12915366) + (2 − rs1317286)]/5. When the coded allele was negatively associated with current smoking status, we coded for the other allele by subtracting the allele dosage from 2.

[d] GRS (genetic risk score) = [(2 − rs2227341) + (2 − rs10418195) + (2 − rs773895) + rs7245967 + (2 − rs2981474)]/5.

Web Table 10. Comparison of descriptive statistics between compliers and non-compliers, assuming 1 or 2 copies of rs4074134 coded allele is "treated" (GENOA; Jackson, Mississippi; 2000–2005)

Variable	**Compliers (*N* = 552, 67%)**	**Noncompliers (*N* = 270, 33%)**	
Continuous	**Mean ± SD**	**Mean ± SD**	***P***
Age at examination (years)	66.67 ± 7.55	66.38 ± 7.45	0.74
BMI (kg/m^2)	31.65 ± 6.52	30.66 ± 6.12	0.052
CRP (mg/L)	1.26 ± 1.05	1.31 ± 1.15	0.46
Interleukin-6 (pg/mL)	2.13 ± 0.57	2.01 ± 0.59	0.44
Interleukin-18 (pg/mL)	4.12 ± 0.61	4.08 ± 0.60	0.51
Fibrinogen (mg/dL)	364.18 ± 77.09	379.62 ± 86.63	0.02
Categorical	**N (%)**	**N (%)**	***P***
Sex (female)	408 (74%)	184 (68%)	0.09

GENOA, Genetic Epidemiology Network of Arteriopathy; SD, standard deviation; BMI, body mass index; CRP, C-reactive protein.

Web Table 11. Distribution of genotypes by smoking status (current, former, and never smoking) (GENOA; Jackson, Mississippi; 2000–2005)

Smoking Status	rs4074134 [a]			χ^2 Test	*P*
	0	1	2		
Current smoking	61	39	4	Current vs. never	0.02
Former smoking	161	70	7	Former vs. never	0.4
Never smoking	348	120	12		
Smoking Status	**rs1964678**			**χ^2 Test**	***P***
	0	**1**	**2**		
Current smoking	65	36	3	Current vs. never	0.02
Former smoking	131	85	22	Former vs. never	0.6
Never smoking	245	187	48		
Smoking Status	**rs952216 [b]**			**χ^2 Test**	***P***
	0	**1**	**2**		
Current smoking	87	17	0	Current vs. never	0.07
Former smoking	176	55	7	Former vs. never	0.87
Never smoking	357	112	11		
Smoking Status	**rs3813571 [c]**			**χ^2 Test**	***P***
	0	**1**	**2**		
Current smoking	86	18	0	Current vs. never	0.06
Former smoking	176	55	7	Former vs. never	0.99
Never smoking	353	113	14		
Smoking Status	**rs1317286**			**χ^2 Test**	***P***
	0	**1**	**2**		
Current smoking	50	40	14	Current vs. never	0.04
Former smoking	134	91	13	Former vs. never	0.62
Never smoking	252	198	30		

GENOA, Genetic Epidemiology Network of Arteriopathy.

[a] rs4074134 is in a high LD ($r^2 > 0.9$) with rs4923457 and rs4923460; hence the cross table was not shown separately.

[b] rs952216 is in a high LD ($r^2 > 0.9$) with rs11636131, rs11632604, rs12910289, rs1504546, and rs12916999; hence the cross table was not shown separately.

[c] rs3813571 is in a high LD ($r^2 > 0.9$) with rs12915366, rs12916483, and rs3813571; hence the cross table was not shown separately.