Supplementary material:
Meta-analysis of up to 622,409 individuals identifies 40 novel smoking behaviour associated genetic loci

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CHDExome+ participating cohorts:

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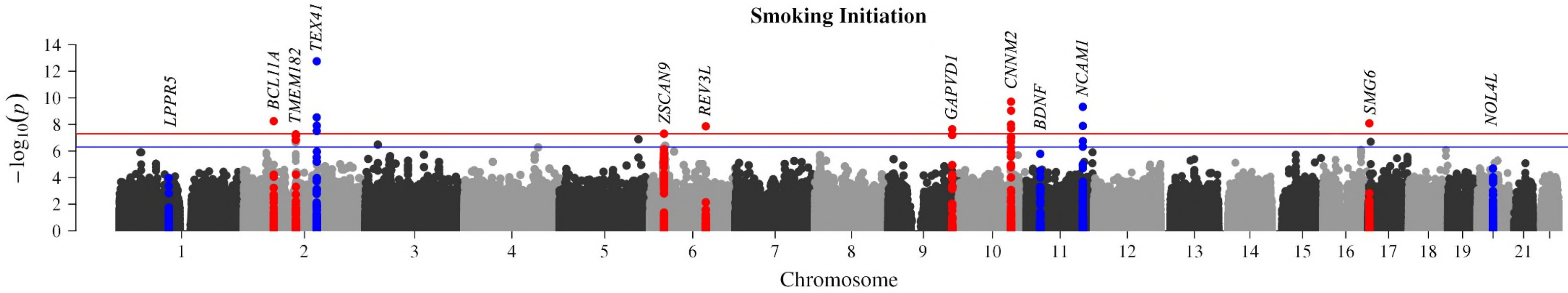
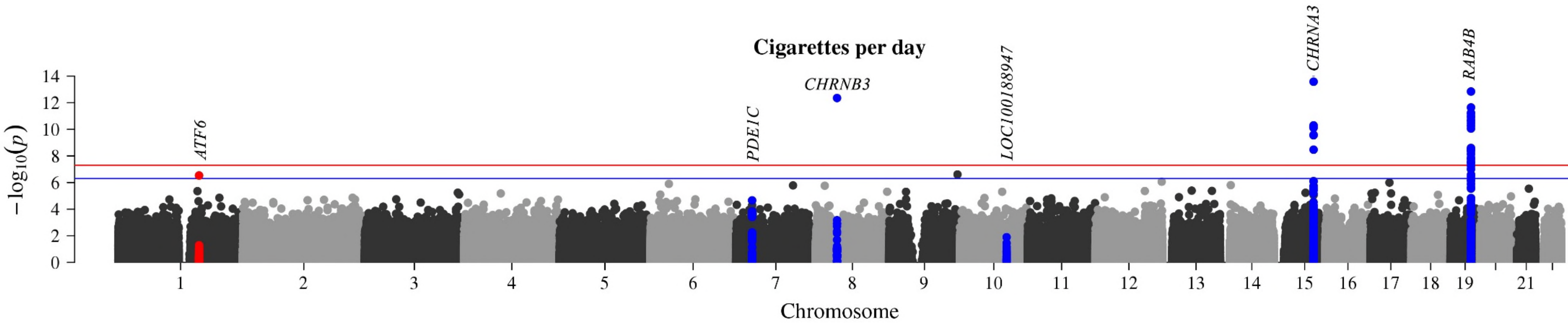
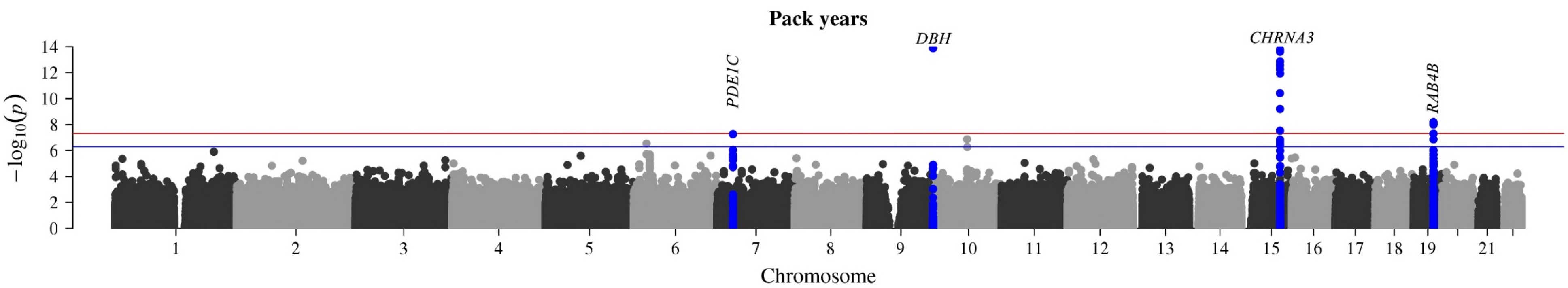
35. Wellcome Trust Sanger Institute, Genome Campus, Hinxton, UK

Figures

Supp. Figures 1a-d: Manhattan plots of all four smoking behaviour related trait association studies (at discovery stage). Plots are shown of genome-wide association results for Smoking cessation (top), Cigarettes per day, Pack-years, and Smoking initiation (bottom). Previously reported signals are shown in dark blue, and new signals are shown in red. Signals are shown only for the trait with which they exhibited the strongest association. The red and blue lines correspond to the genome-wide significance level (P=5×10^{-8}; $-\log_{10}P$=7.3) and suggestive significance (P=5×10^{-7}; $-\log_{10}P$=6.3), respectively. Labels are for the nearest gene to the new sentinel variants. The top signals were truncated at 10^{-14} for clarity. The image was created using a modified version of the R package qqman. NB: SNVs in/near *REV3L*, *CNNM2* and *TMEM182* replicated in the replication stage (for SI).







Pack years
DBH
CHRNA3
PDE1C
RAB4B
−log10(p)
14
12
10
8
6
4
2
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
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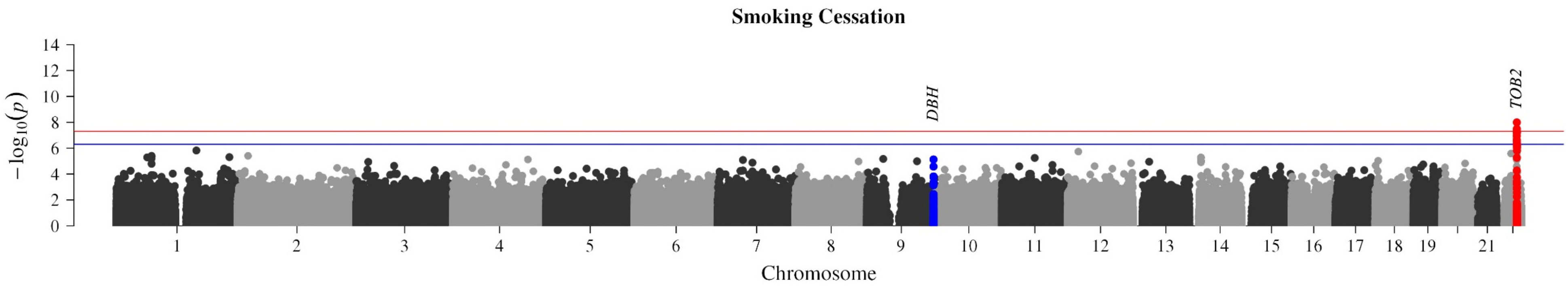
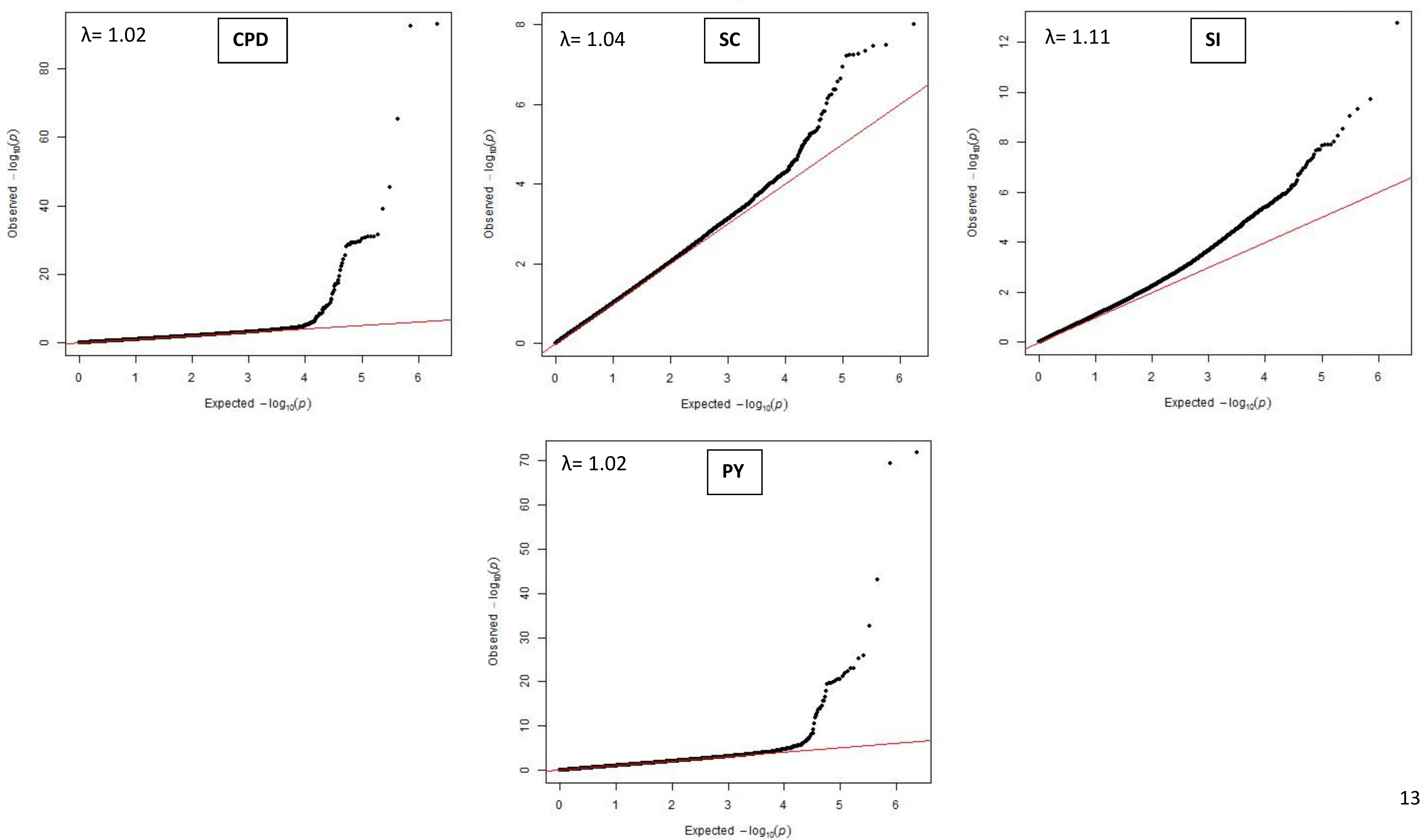
16
17
18
19
21
Chromosome



Smoking Cessation
DBH
TOB2
−log10(p)
14
12
10
8
6
4
2
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
21
Chromosome

Supp. Figures 2a-d: Quantile-Quantile (QQ)-plots and genomic inflation factor (λ) for Smoking Initiation (SI), Smoking Cessation (SC), Cigarettes per day (CPD), and Pack-years (PY) meta-analyses (discovery stage).



Tables

Supp. Table 1: Studies which contributed to primary analyses (at discovery stage), the consortia name, and sample size, gender distribution and ancestry of each dataset. CGSB: Consortium for the Genetics of Smoking Behaviour (Leicester); CHDExome+: Coronary Heart Disease Exome+ consortium (Cambridge); GSCAN: GWAS & Sequencing Consortium of Alcohol and Nicotine (Colorado & Michigan). Affiliation with same consortia implies that a similar study-level QC protocol and analysis plan was followed. DNC: Did not contribute or excluded due to quality control issues; n: sample size; N/A: information not available.

	Cohort/Sample collections	**Consortia**	**Smoking initiation n (smokers/non-smokers)**	**Cigarettes per day n (mean/sd)**	**Pack-years n (mean/sd)**	**Smoking cessation n (current smokers/ex-smokers)**	**Gender distribution for Smoking initiation samples (Male/Female)**	**Ancestry of samples**
1	Airwave	CGSB	1905 (556/1349)	160 (9.5/6.5)	556 (10.2/9.5)	556 (396/160)	1210/695	White European
2	ASCOT – Scotland dataset	CGSB	2461 (1737/724)	1029 (12.9/7.9)	DNC	1738 (688/1070)	1833/629	White European
3	ASCOT – UK dataset	CGSB	3243 (2267/976)	725 (13.2/9.6)	DNC	2267 (1462/805)	2659/587	White European
4	1958BC	CGSB	5537 (2943/2594)	2839 (18.72/10.21)	2258 (16.93/10.7)	2738 (1078/1660)	3264/2553	White European
5	BRIGHT	CGSB	851 (401/450)	376 (17.2/11.2)	360 (23.5/19.8)	401 (287/114)	508/851	White European
6	DIABNORD	CGSB	397 (175/222)	DNC	DNC	175 (88/87)	193/204	White European
7	EFSOCH	CGSB	1389 (689/700)	385 (10.32/9.9)	DNC	208 (100/108)	701/688	White European
8	EGCUT – BMI dataset	CGSB	929 (506/423)	DNC	500 (15.7/14.6)	DNC	464/465	White European
9	EGCUT – Controls dataset	CGSB	807 (304/529)	293 (13.42/8.86)	292 (12.82/13.75)	294 (149/155)	407/400	White European
10	EGCUT - Height cases dataset	CGSB	DNC	429 (12.91/7.68)	421 (12.07/13.72)	432 (129/306)	N/A	White European
11	EGCUT – Psoriasis cases dataset	CGSB	DNC	409 (12.19/8.11)	407 (10.08/11.54)	414 (257/157)	N/A	White European
12	EGCUT - T2D cases dataset	CGSB	836 (347/507)	DNC	DNC	337 (195/152)	366/470	White European
13	EGCUT – CoreExome dataset	CGSB	4642 (1955/2687)	1904 (10.67/7.29)	1884 (6.22/7.63)	1955 (503/1452)	1518/3124	White European
14	EMBRACE	CGSB	604 (296/308)	290 (11.72/7.17)	286 (12.47/11.61)	295 (198/97)	0/604	White European

15	Fenland	CGSB	1333 (632/701)	425 (11.4/9.1)	290 (12.7/13.0)	632 (443/189)	619/714	White European
16	FIA3	CGSB	2387 (1429/958)	DNC	DNC	1429 (491/938)	1612/775	White European
17	GS:SFHS	CGSB	9810 (4705/5105)	2511 (14.19/9.64)	4824 (18.07/18.76)	4470 (2916/1554)	5760/4050	White European
18	GLACIER	CGSB	928 (432/496)	DNC	DNC	432 (226/206)	420/508	White European
19	GoDARTS	CGSB	4447 (2746/1701)	2578 (7.72/5.1)	2575 (18.45/13.33)	2745 (720/2025)	2673/1774	White European
20	KORA F4	CGSB	2843 (1664/1179)	443 (15.24/8.75)	1591 (29.81/21.33)	1680 (1155/525)	1378/1465	White European
21	CROATIA-Korcula	CGSB	836 (430/406)	415 (19.42/14.55)	415 (21.20/26.04)	410 (222/195)	523/313	White European
22	LBC1921	CGSB	503 (284/219)	283 (15.43/11.02)	280 (28.14/24.37)	284 (247/37)	208/295	White European
23	LBC1936	CGSB	983 (527/456)	518 (17.61/12.61)	516 (31.04/27.37)	527 (421/106)	498/485	White European
24	LifeLines	CGSB	DNC	1012 (11.35/9.54)	1036 (13.7/11.34)	1058 (578/480)	N/A	White European
25	LOLIPOP Exome chip dataset	CGSB	1664 (301/1363)	1663 (11.5/8.78)	1636 (14.94/13.85)	301 (157/144)	1241/423	White European
26	LOLIPOP OmniExpress chip dataset	CGSB	977 (158/819)	975 (10.45/10.34)	961 (12.41/13.81)	158 (73/85)	560/417	White European
27	LRGP	CGSB	2070 (1620/441)	389 (14.42/8.11)	987 (16.91/10.27)	2061 (668/952)	1065/1335	White European
28	OxBB	CGSB	4301 (1701/2600)	1698 (11.6/9.01)	1652 (15.3/14.78)	1719 (1229/490)	2010/2291	White European
29	SEARCH – Breast Cancer dataset	CGSB	3465 (1722/1743)	534 (13.65/7.33)	1616 (16.71/12.77)	1722 (757/965)	0/3465	White European
30	SEARCH – Controls dataset	CGSB	1810 (839/971)	206 (12.89/7.33)	777 (18.66/15.46)	839 (598/241)	958/852	White European
31	SEARCH – Ovarian Cancer dataset	CGSB	723 (298/425)	56 (14.52/6.97)	270 (17.65/14.78)	298 (204/94)	0/723	White European
32	SHIP	CGSB	7396 (3484/3912)	1875 (14.49/7.66)	3465 (18.81/15.92)	3484 (1609/1875)	3573/3823	White European
33	SIBS	CGSB	878 (392/486)	375 (12.7/8.04)	375 (16.04/6.18)	392 (306/86)	0/878	White European
34	UKHLS	CGSB	9176 (5111/4185)	1712 (13.75/8.16)	2683 (20.23/21.63)	5111 (3338/1773)	4086/5210	White European
35	ARIC	GSCAN	8970	5381	5304	DNC	N/A	White European
36	COGA	GSCAN	DNC	1465	1435	DNC	N/A	White European
-	COGA - replication	GSCAN	DNC	476	476	DNC	N/A	African American
37	FTC	GSCAN	1467	819	767	DNC	275/1192	White European
38	FUSION	GSCAN	1153	568	530	DNC	N/A	White European
39	GECCO	GSCAN	6459	2916	2876	DNC	N/A	White European
40	GFG	GSCAN	2994	1396	432	DNC	N/A	White European

41	HRS	GSCAN	6393	3303	3303	DNC	N/A	White European
-	HRS – replication	GSCAN	DNC	961	961	DNC	N/A	African American
42	ID1000	GSCAN	803	366	373	DNC	N/A	White European
43	MEC	GSCAN	1903	1087	1082	DNC	396/1507	White European
44	METSIM	GSCAN	8146	1374	1370	DNC	8146/0	White European
45	MHI	GSCAN	6820	4391	4400	DNC	1950/4870	White European
46	MN	GSCAN	DNC	2043	DNC	DNC	N/A	White European
47	NAGOZALC	GSCAN	1038	671	646	DNC	187/851	White European
48	NESCOG	GSCAN	486	217	220	DNC	N/A	White European
49	sardiNIA	GSCAN	5069	1969	1967	DNC	N/A	White European
50	TwinsUK	GSCAN	878	358	358	DNC	N/A	White European
51	UK Biobank (non-UK BiLEVE subset)	GSCAN	73331	21525	21267	31748 (18084/13664)	16538/56793	White European
52	UK BiLEVE	GSCAN	39480	19357	19357	19295(12836/6459)	9945/29535	White European
53	WHI	GSCAN	DNC	6246	6236	DNC	2994	White European
54	CCHS	CHDExome+	6287 (4021/2266)	DNC	DNC	4010 (83/3927)	N/A	White European
55	CGPS	CHDExome+	11781 (7555/4226)	DNC	DNC	7541 (4299/3242)	N/A	White European
56	CIHDS	CHDExome+	3434 (2074/1360)	DNC	DNC	DNC	N/A	White European
57	EPIC-CVD	CHDExome+	21475 (12477/8998)	4680 (15.58/10.06)	4548 (25.77/18.65)	6015 (217/5798)	N/A	White European
58	INTERVAL	-	36479 (15354/21125)	14124 (9.85/7.72)	12782 (8.59/10.25)	15264 (12228/3036)	N/A	White European
59	PROSPER	CHDExome+	1279 (880/399)	DNC	DNC	910 (588/322)	N/A	White European
60	PROMIS	CHDExome+	21831 (10008/11823)	7913 (15.97/11.71)	7623 (22.92/19.69)	8509 (171/8338)	N/A	South Asian
61	BRAVE	CHDExome+	5543 (4252/1291)	3144 (12.68/8.96)	3090 (18.20/15.90)	4022 (349/3673)	N/A	South Asian
62	MORGAM	CHDExome+	DNC	2684 (18.50/9.01)	DNC	DNC	N/A	White European
-	**Total**	-	55 cohorts	53 cohorts	49 cohorts	42 cohorts	-	-

Supp. Table 2: Studies which contributed to primary analyses (at discovery stage), the consortia name, sample size of each dataset, and details of study specific genotyping platform and software used. CGSB: Consortium for the Genetics of Smoking Behaviour (Leicester); CHDExome+: Coronary Heart Disease Exome+ (Cambridge); GSCAN: GWAS & Sequencing Consortium of Alcohol and Nicotine (Colorado & Michigan). Affiliation with same consortia implies that a similar QC protocol and analysis plan was followed. DNC: Did not contribute; n: sample size; PC: principal component.

	Cohort	Consortia	Genotyping Platform	Study-level software	Covariates used	Transformations	Analysis model
1	Airwave	CGSB	HumanExome v1.1	RareMetalWorker	Age, sex and top 4 PCs	Where available (see Supp. Table 1), quantitative traits (i.e. CPD and PY) were inverse normalised	CPD and PY were analysed using linear regression; and SI and SC were analysed using logistic regression
2	ASCOT – Scotland dataset	CGSB	Human OmniExpressExome v8.1	RareMetalWorker	Age, sex and top 10 PCs		
3	ASCOT – UK dataset	CGSB	HumanExome v1.1	RareMetalWorker	Age, sex and top 10 PCs		
4	1958BC	CGSB	HumanExome v1.0	RareMetalWorker	Age, sex and top 3 PCs		
5	BRIGHT	CGSB	HumanExome v1.0	RareMetalWorker	Age, sex and top 10 PCs		
6	DIABNORD	CGSB	HumanExome v1.1	RareMetalWorker	Age, sex and top 3 PCs		
7	EFSOCH	CGSB	HumanExome v1.0	RareMetalWorker	Age, sex and top 3 PCs		
8	EGCUT – BMI dataset	CGSB	HumanExome v1.1	RareMetalWorker	Age, sex and top 10 PCs		
9	EGCUT – Controls dataset	CGSB	HumanExome v1.1	RareMetalWorker	Age, sex and top 10 PCs		
10	EGCUT - Height cases dataset	CGSB	HumanExome v1.1	RareMetalWorker	Age, sex and top 10 PCs		
11	EGCUT – Psoriasis cases dataset	CGSB	HumanExome v1.1	RareMetalWorker	Age, sex and top 10 PCs		
12	EGCUT - T2D cases dataset	CGSB	HumanExome v1.1	RareMetalWorker	Age, sex and top 10 PCs		
13	EGCUT – CoreExome dataset	CGSB	HumanCoreExome v1.1	RareMetalWorker	Age, sex and top 10 PCs		
14	EMBRACE	CGSB	Illumina ExomeChip v1.0	RareMetalWorker	Age and top 3 PCs		
15	Fenland	CGSB	HumanExome v1.0	RareMetalWorker	Age, sex and top 10 PCs		
16	FIA3	CGSB	HumanExome v1.1	RareMetalWorker	Age, sex and top 10 PCs		
17	GS:SFHS	CGSB	HumanExome v1.0	RareMetalWorker	Age, sex and top 3 PCs		
18	GLACIER	CGSB	HumanExome v1.1	RareMetalWorker	Age, sex and top 3 PCs		
19	GoDARTS	CGSB	HumanExome v1.0	RareMetalWorker	Age, sex and top 3 PCs		

20	KORA F4	CGSB	HumanExome v1.0	RareMetalWorker	Age, sex and top 10 PCs		
21	CROATIA-Korcula	CGSB	HumanExome v1.0	RareMetalWorker	Age, sex and top 3 PCs		
22	LBC1921	CGSB	HumanExome v1.0	RareMetalWorker	Age, sex and top 10 PCs		
23	LBC1936	CGSB	HumanExome v1.0	RareMetalWorker	Age, sex and top 10 PCs		
24	LifeLines	CGSB	HumanExome v1.1	RareMetalWorker	Age, sex and top 5 PCs		
25	LOLIPOP Exome chip dataset	CGSB	HumanExome v1.1	RareMetalWorker	Age, sex and top 3 PCs		
26	LOLIPOP OmniExpress chip dataset	CGSB	Human OmniExpressExome v8.1	RareMetalWorker	Age, sex and top 3 PCs		
27	LRGP	CGSB	HumanExome v1.1	RareMetalWorker	Age, sex and top 3 PCs		
28	OxBB	CGSB		RareMetalWorker	Age, sex and top 10 PCs		
29	SEARCH – Breast Cancer dataset	CGSB	HumanExome v1.0	RareMetalWorker	Age and top 3 PCs		
30	SEARCH – Controls dataset	CGSB	HumanExome v1.0	RareMetalWorker	Age, sex and top 3 PCs		
31	SEARCH – Ovarian Cancer dataset	CGSB	HumanExome v1.0	RareMetalWorker	Age and top 3 PCs		
32	SHIP	CGSB	HumanExome v1.0	RareMetalWorker	Age, sex and top 10 PCs		
33	SIBS	CGSB	HumanExome v1.0	RareMetalWorker	Age and top 3 PCs		
34	UKHLS	CGSB	HumanCoreExome v1.0	RareMetalWorker	Age, sex and top 10 PCs		
35	ARIC	GSCAN	HumanExome v1.0	RareMetalWorker	Age, sex and top 3 PCs	CPD was a categorical trait (1-4) with responses binned at 1-10 (1), 11-20 (2), 21-30 (3), and 31+ (4). The residuals for the quantitative traits were transformed using inverse normal transformation	
36	COGA	GSCAN	HumanCoreExome v1.0	RareMetalWorker	Age, sex and top 3 PCs		
37	FTC	GSCAN	HumanCoreExome v1.0	Rvtests	Age, age^2, sex, BMI, assessment year and top 3 PCs		
38	FUSION	GSCAN	HumanExome v1.0	RareMetalWorker	Age, sex and top 3 PCs		
39	GECCO	GSCAN	HumanExome v1.0	RareMetalWorker	Age, sex and top 3 PCs		
40	GFG	GSCAN	Illumina HumanCoreExome array with custom content	Rvtests	Age, age^2, sex and top 3 PCs		
41	HRS	GSCAN	HumanExome v1.0	RareMetalWorker	Age, sex and top 3 PCs		

-	HRS - replication	GSCAN	HumanExome v1.0	RareMetalWorker	Age, sex and top 10 PCs		
42	ID1000	GSCAN	HumanExome v1.0	RareMetalWorker	Age, sex and top 3 PCs		
43	MEC	GSCAN	HumanExome v1.0	RareMetalWorker	Age, sex and top 10 PCs		
44	METSIM	GSCAN	HumanExome v1.0	RareMetalWorker	Age, sex and top 3 PCs		
45	MHI	GSCAN	HumanExome v1.0	Rvtests	Age, age^2, sex, enrolment date and top 10 PCs		
46	MN	GSCAN	HumanExome v1.0	RareMetalWorker	Age, sex and top 3 PCs		
47	NAGOZALC	GSCAN	HumanCNV370-quad V3	RareMetalWorker	Age, sex and top 3 PCs		
48	NESCOG	GSCAN	HumanExome v1.0	RareMetalWorker	Age, sex and top 3 PCs		
49	sardiNIA	GSCAN	HumanExome v1.0	RareMetalWorker	Age, sex and top 3 PCs		
50	TwinsUK	GSCAN	HumanExome v1.0	RareMetalWorker	Age, sex and top 3 PCs		
51	UK Biobank (non-UK BiLEVE subset)	GSCAN	UK Biobank Axiom Array	Rvtests	Age, age^2, sex and top 10 PCs		
52	UK BiLEVE	GSCAN	UK BiLEVE Axiom Array	Rvtests	Age, age^2, sex and top 10 PCs		
53	WHI	GSCAN	HumanExome v1.0	RareMetalWorker	Age, sex and top 3 PCs		
54	CCHS	CHDExome+	HumanExome v1.1	RareMetalWorker	Age, sex and top 3 PCs	Where available (see Supp. Table 1), quantitative traits were inverse normalised	All traits were analysed using linear mixed models
55	CGPS	CHDExome+	HumanExome v1.1	RareMetalWorker	Age, sex and top 3 PCs		
56	CIHDS	CHDExome+	HumanExome v1.1	RareMetalWorker	Age, sex and top 3 PCs		
57	EPIC-CVD	CHDExome+	HumanExome v1.1	RareMetalWorker	Age, sex and top 3 PCs		
58	INTERVAL	-	UK Biobank Axiom Array	RareMetalWorker	Age, age^2, sex, blood donation centre, BMI and top 3 PCs		
59	PROSPER	CHDExome+	HumanExome v1.1	RareMetalWorker	Age, sex and top 3 PCs		
60	PROMIS (South Asian samples)	CHDExome+	HumanExome v1.1	RareMetalWorker	Age, sex and top 3 PCs		
61	BRAVE (South Asian samples)	CHDExome+	HumanExome v1.1	RareMetalWorker	Age, sex and top 3 PCs		
62	MORGAM	CHDExome+	HumanExome v1.1	RareMetalWorker	Age, sex and top 3 PCs		
-	**Meta-analysis**	-	-	RAREMETAL			

Supp. Table 3: Association of the 14 SNPs previously identified smoking behaviour loci in the discovery stage cohorts. For each variant, the result is presented for the smoking behaviour related trait for which it was first reported. SNPs with $P<5\times10^{-8}$ are in **bold**. r^2: r^2 value between the Exome chip proxy SNP and the previously reported SNP in White European samples of the 1000 Genomes project; non-Ex: Non- Exome chip SNP; NA: A proxy SNP could not be found for the previously reported SNP ($r^2\geq0.3$); SI: Smoking initiations; SC: Smoking cessation; CPD: Cigarettes per day; PY: Pack-years.

Reported SNP ID (effect/alternative allele)	Chr:Pos (hg19)	Exome-chip proxy or UK Biobank Axiom Array SNP ID	Proxy Chr:Pos	Proxy SNP effect/ alternative allele (consequence)	Gene	Trait	Discovery P-value of proxy SNP	Replication stage P-value (beta/se)	Combined meta-analysis P-value of proxy SNP	r^2	References
rs1051730 (A/G)	15:78894339	rs1051730	15:78894339	A/G (synonymous)	15q25 (*CHRNA3*)	CPD	**2.17×10^{-32}**	**2.6×10^{-81}** (0.101/ 0.0052)	**5.5×10^{-121}**	Same SNP	The Tobacco and Genetics Consortium, 2010[6]
						PY	**2.83E-21**	NA	NA	-	-
rs215605 (G/T)	7:32336965	rs215607	7:32338337	A/G (missense)	7p14 (*PDE1C*)	CPD	0.017	0.024 (-0.013/ 0.0059)	9.0×10^{-4}	0.46	Thorgeirsson *et al*, 2010[7]
						PY	5.5×10^{-8}	NA	NA	-	-
rs13280604 (G/A)	8:42559586	rs6474412	8:42550498	T/C (intergenic)	8p11 (*CHRNB3*)	CPD	**1.3×10^{-11}**	**9.8×10^{-13}** (0.043/ 0.0060)	**2.2×10^{-21}**	1	Thorgeirsson *et al*, 2010[7]
						PY	1.25×10^{-5}	NA	NA	-	-
rs1329650 (G/T)	10:93348120	rs1329650	10:93348120	G/T (intergenic)	*LOC100188947*	CPD	0.068	0.51 (0.0037/ 0.0056)	0.081	Same SNP	The Tobacco and Genetics Consortium, 2010[6] & Thakur *et al*, 2012[8]
						PY	0.063	NA	NA	-	-
rs3733829 (G/A)	19:41310571	rs3733829	19:41310571	G/A (intronic)	*EGLN2*	CPD	0.00022	1.1×10^{-6} (0.025/ 0.0052)	**1.66×10^{-9}**	Same SNP	The Tobacco and Genetics Consortium, 2010[6] & Bloom *et al*, 2014[9]
						PY	0.016	NA	NA	-	-
rs7937 (C/T)	19:41302706	rs7937	19:41302706	C/T (intronic)	19q13 (*RAB4B*)	CPD	**5.35×10^{-11}**	**8.7×10^{-14}** (-0.037/ 0.0050)	NA	Same SNP	Thorgeirsson *et al*, 2010[7] & Timofeeva *et al*, 2011[10]
						PY	**8.18×10^{-9}**	NA	NA	-	-
rs3025343 (A/G)	9:136478355	rs3025343	9:136478355	A/G (intergenic)	*DBH*	SC	0.00028	**3.2×10^{-10}** (0.039/ 0.0062)	**3.94×10^{-12}**	Same SNP	The Tobacco and Genetics Consortium, 2010[6] & Siedlinski *et al*, 2011[11]
rs6265 (T/C)	11:27679916	rs6265	11:27679916	T/C (missense)	*BDNF*	SI	8.59×10^{-6}	**2.9×10^{-8}** (-0.019/ 0.0034)	**8.43×10^{-12}**	Same SNP	The Tobacco and Genetics Consortium, 2010[6]

rs4466874 (C/T)	11:112861434	rs4144892 (non-Ex)	11:112866456	T/C (intronic)	*NCAM1*	SI	**$4.7x10^{-10}$**	**$6.1x10^{-17}$** (0.023/ 0.0027)	**$7.26x10^{-25}$**	1	Wain *et al*, 2015[12]
rs10193706 (C/A)	2:146316319	rs10427255	2:146125523	T/C (intergenic)	*TEX41/PABPC1P2*	SI	**$3.06x10^{-14}$**	**$6.2x10^{-10}$** (-0.0166/ 0.0027)	**$2.97x10^{-22}$**	0.40	Wain *et al*, 2015[12]
rs61784651 (T/C)	1:99445471	rs61784651 (non-Ex)	1:99445471	T/C (intergenic)	*LPPR5*	SI	0.00010	$3.3x10^{-3}$ (0.0105/ 0.0036)	0.0071	Same SNP	Wain *et al*, 2015[12]
rs10807199 (T/C)	6:38901867	rs9296270 (non-Ex)	6:38903095	A/G (intronic)	*DNAH8*	SI	0.0012	0.74 (0.0009/ 0.0027)	0.0109	1	Wain *et al*, 2015[12]
rs143125561 (C/CACGG)	20:31162590-31162591	rs4911241	20:31140165	T/C (intronic)	*NOL4L*	SI	$7.22x10^{-5}$	$6.4x10^{-8}$ (0.0170/ 0.0031)	**$2.94x10^{-10}$**	0.91	Wain *et al*, 2015[12]
rs2273500 (C/T)	20:61986949	rs2273506	20:61990939	A/G (synonymous)	*CHRNA4*	Fagerström test (CPD)	$5.41x10^{-5}$	0.003 (0.030/ 0.0101)	$8.92x10^{-7}$	0.40	Hancock *et al*, 2015[13] (& Wain *et al*, 2015[12])

Supp. Table 4: Results from sensitivity analyses, and consortium-specific association studies for each novel SNP (discovery stage). CHDExome+ consortium did not contribute to X chromosome analyses. Same: Same *P*-value as in Primary analysis. MAC, effect size (β) and 95% confidence interval (CI) of rs141611945 (*ATF6*) added for additional information on this rare SNP – to add evidence as (internal) replication. * The rare nonsynonymous *ATF6* SNV, rs141611945, associated with CPD in the discovery stage of this study, was only polymorphic in six studies, with a total MAC=9 across all 129,000 individuals. The variant was not available in UK Biobank. rs141611945 is more common in African ancestries (1.2%), but we were unable to ascertain sufficient numbers of African-ancestry individuals (n=1,437) to replicate the association.

Trait	Gene	SNP ID	Chr:Pos	*P*-value in Primary analysis	*P*-value excluding all UK Biobank samples	*P*-value excluding all UK Biobank and South Asian samples	*P*-value in CGSB	*P*-value in GSCAN	*P*-value in CHDExome+ plus INTERVAL samples	*P*-value in South Asian samples only	*P*-value excl. UK BiLEVE samples
CPD	*ATF6**	rs141611945	1:161771868	2.95×10^{-7} (n=128,746; β=1.71; 95% CI: 2.36-1.05)	Same	Same	0.00017 (n=26,506, MAC=6; β=1.53; 95% CI: 2.33-0.73)	0.0053 (n=69,695, MAC=2; β=1.97; 95% CI: 3.36-0.59)	0.025 (n=32,545, MAC=1; β=2.24; 95% CI: 4.24-0.28)	NA	NA
CPD	*GPR101*	rs1190736	X:136113464	$\mathbf{1.40\times10^{-11}}$ (n=99,037)	3.28×10^{-7} (n=90,398)	Same as left	0.0010 (n=26,499)	$\mathbf{3.42\times10^{-9}}$ (n=51,050)	NA	NA	NA
SI	*REV3L*	rs462779	6:111695887	$\mathbf{4.52\times10^{-8}}$ (n=346,682)	1.62×10^{-6} (n=233,871)	3.14×10^{-7} (n=212,040)	1.20×10^{-5} (n=78,048)	0.0013 (n=165,368)	0.0247 (n=103,266)	0.754 (n=21,831)	NA
SI	*SMG6*	rs216195	17:2203167	$\mathbf{2.80\times10^{-8}}$ (n=335,406)	3.34×10^{-7} (n=222,595)	8.22×10^{-8} (n=200,937)	0.0013 (n=78,056)	2.04×10^{-5} (n=154,822)	0.00245 (n=102,528)	0.542 (n=21,658)	NA
SI	*PJA1*	rs11539157	X:68381264	$\mathbf{1.39\times10^{-11}}$ (n=289,917)	$\mathbf{4.53\times10^{-9}}$ (n=230,072)	Same as left	8.73×10^{-7} (n=78,040)	3.09×10^{-7} (n=108,512)	NA	NA	NA
Non-Exome chip SNVs											
SI	*TMEM182*	rs12616219	2:104352495	5.49×10^{-8} (n=112,811)	NA	NA	NA	Same	NA	NA	0.00027
SI	*ZSCAN9*	rs462779	6:28168033	$\mathbf{4.95\times10^{-8}}$ (n=112,811)	NA	NA	NA	Same	NA	NA	0.00051
SI	*GAPVD1*	rs2841334	9:128122320	$\mathbf{2.28\times10^{-8}}$ (n=112,811)	NA	NA	NA	Same	NA	NA	5.26×10^{-5}
SC	*TOB2*	rs202664	22:41813886	$\mathbf{1.02\times10^{-8}}$ (n=51,043)	NA	NA	NA	Same	NA	NA	2.89×10^{-7}
SI	*BCL11A*	rs11895381	2:60053727	$\mathbf{5.62\times10^{-9}}$ (n=112,811)	NA	NA	NA	Same	NA	NA	4.44×10^{-6}
SI	*CNNM2*	rs12780116	10:104821946	$\mathbf{9.19\times10^{-10}}$ (n=112,811)	NA	NA	NA	Same	NA	NA	9.61×10^{-5}

Supp. Table 5: Single variant association results for all novel and previously reported SNVs across all four traits (discovery stage). SNVs which reach $P<5x10^{-8}$ are highlighted in **bold**. NA: Reported SNP (or a proxy) not available in our study. Direction of effect provided in parentheses for all variants reaching $P<0.05$.

Reported SNP ID (effect/alternative allele)	**Chr:Pos (hg19)**	**Gene**	***P*-value for SI** (direction of effect)	***P*-value for CPD** (direction of effect)	***P*-value for PY** (direction of effect)	***P*-value for SC** (direction of effect)	**Notes**
Novel SNVs identified in this study							
rs141611945 (G/A)	1:161771868	*ATF6*	0.58	$2.95x10^{-7}$ (+)	0.00015 (+)	0.866	-
rs1190736 (A/C)	X:136113464	*GPR101*	0.13	**$1.40x10^{-11}$** (-)	**$4.98x10^{-9}$** (-)	0.503	-
rs462779 (A/G)	6:111695887	*REV3L*	**$4.52x10^{-8}$** (-)	0.651	0.545	0.042 (+)	-
rs216195 (G/T)	17:2203167	*SMG6*	**$2.80x10^{-8}$** (-)	0.378	0.628	0.446	-
rs11539157 (A/C)	X:68381264	*PJA1*	**$1.40x10^{-11}$** (+)	0.087	0.0017 (+)	0.034 (-)	-
rs12616219 (A/C)	2:104352495	*TMEM182*	$5.49x10^{-8}$ (-)	0.495	0.814	0.201	-
rs1150691 (G/A)	6:28168033	*ZSCAN9*	**$4.95x10^{-8}$** (-)	0.523	0.499	0.415	-
rs2841334 (A/G)	9:128122320	*GAPVD1*	**$2.28x10^{-8}$** (-)	0.088	0.260	0.0081 (-)	-
rs202664 (C/T)	22:41813886	*TOB2*	0.26	0.865	0.416	**$1.02x10^{-8}$** (-)	-
rs11895381 (A/G)	2:60053727	*BCL11A*	**$5.62x10^{-9}$** (-)	0.467	0.268	0.491	-
rs12780116 (A/G)	10:104821946	*CNNM2*	**$9.19x10^{-10}$** (+)	0.305	0.635	0.884	-
Previously reported SNVs							
rs1051730 (A/G)	15:78894339	15q25 (*CHRNA3*)	0.23	**$2.17x10^{-32}$** (+)	**$2.83x10^{-21}$** (+)	0.043 (+)	-
rs215605 (G/T)	7:32336965	7p14 (*PDE1C*)	0.014 (+)	0.0099 (+)	**$5.41x10^{-6}$** (+)	0.033 (+)	Results for rs215607 provided in **Supp. Table 3**
rs13280604 (G/A)	8:42559586	8p11 (*CHRNB3*)	0.49	0.0012 (-)	0.064	0.97	-
rs1329650 (T/G)	10:93348120	*LOC100188947*	0.010 (-)	0.068	0.063	0.40	-
rs3733829 (G/A)	19:41310571	*EGLN2*	0.48	0.00022 (+)	0.016 (+)	0.936	-
rs7937 (T/C)	19:41302706	19q13 (*RAB4B*)	0.75	**$5.35x10^{-11}$** (+)	**$8.18x10^{-9}$** (+)	0.0054 (-)	-
rs3025343 (A/G)	9:136478355	*DBH*	0.010 (+)	**$2.93x10^{-9}$** (+)	**$1.29x10^{-14}$** (+)	0.00028 (-)	-
rs6265 (T/C)	11:27679916	*BDNF*	$8.59x10^{-6}$ (-)	0.028 (-)	0.0087 (-)	0.228	-
rs4466874 (C/T)	11:112861434	*NCAM1*	**$4.73x10^{-10}$** (+)	0.675	0.398	0.108	Results are for rs4144892 (r^2= 1; T/C)
rs10193706 (C/A)	2:146316319	*TEX41/PABPC1P2*	**$3.07x10^{-14}$** (-)	0.955	0.176	0.522	Results are for rs10427255 (r^2= 0.49; T/C)
rs61784651 (T/C)	1:99445471	*LPPR5*	0.0001 (+)	0.121	0.580	0.689	-
rs10807199 (T/C)	6:38901867	*DNAH8*	0.00125 (+)	0.896	0.612	0.754	Results are for rs9296270 (r^2= 1; A/G)
rs143125561 (C/CACGG)	20:31162590-31162591	*NOL4L*	NA	NA	NA	NA	-
rs2273500 (C/T)	20:61986949	*CHRNA4*	0.749	$5.41x10^{-5}$ (+)	0.00092 (+)	0.511	Results are for rs2273506 (r^2= 0.32; A/G)

Supp. Table 6: Results for the top four genes from gene-based analyses. *P*-values obtained from each of the collapsing methods utilised, and the variants which were collapsed to produce the overall 'Gene *P*-value' are provided. RsIDs of variants with a MAF>0.01 were included. PY: Pack-years; WST: Weighted sum test; DoE: Direction of effect from the burden test. Conditional analyses were performed to ascertain if the associations below were attributable to more than one SNV. The SNV used to condition on (which is the SNV with the smallest *P*-value in the gene) is listed in 'SNV to condition on'.

Trait	**Gene**	**SNVs for gene tests**	**MAF**	**SNV *P***	**Gene *based test P*-value**		**Conditional gene-based tests MAF=0.05**	
					MAF<0.05 [DoE]	**MAF<0.01**	**SNV to condition on**	***P*-values MAF<0.05 (MAF<0.01)**
CPD	*CRCP*	7:65617235:T:C	4.00E-04	0.0413	Burden: 7.24×10^{-4} WST: 1.94×10^{-4} SKAT: 0.0177 [-]	Burden: 7.24×10^{-4} WST: 1.94×10^{-4} SKAT: 0.0177 [-]	7:65617261	Burden: 9.37×10^{-3} (9.37×10^{-3}) WST: 4.31×10^{-3} (4.31×10^{-3}) SKAT: 0.0333 (0.0333)
		7:65617261:A:G	1.00E-04	0.0128				
		7:65617327:G:A	8.00E-05	0.0406				
CPD	*CHRNA5*	15:78873272:T:G	2.76E-04	0.3075	Burden: **3.38×10^{-8}** WST: 1.57×10^{-4} SKAT: **2.56×10^{-8}** [+]	Burden: 0.0741 WST: 0.0479 SKAT: 0.416	rs2229961	Burden: 0.28 (0.084) WST: 0.0521 (0.05) SKAT: 0.75 (0.51)
		15:78880752:G:A (rs2229961)	0.0167	2.67E-08				
		15:78882233:A:G	3.46E-05	0.7181				
		15:78882331:A:G	1.45E-04	0.7805				
		15:78882446:C:T	1.60E-04	0.5017				
		15:78882682:C:G	4.43E-05	0.3140				
		15:78882694:A:G	1.65E-04	0.2746				
		15:78882726:C:T	2.01E-04	0.1565				
		15:78882797:T:C	3.94E-04	0.3795				
		15:78882821:T:A	1.86E-04	0.1655				
		15:78882920:C:T	2.29E-05	0.9233				
		15:78882934:C:T	8.25E-06	0.3324				
		15:78885574:T:A (rs76071148)	0.0176	0.7520				
PY	*MMP17*	12:132322801:C:A	2.22E-05	0.7454	Burden: 2.28×10^{-5} WST: 8.50×10^{-4} SKAT: 6.44×10^{-4} [-]	Burden: 4.96×10^{-3} WST: 0.0103 SKAT: 0.0725	rs4964883	Burden: 4.45×10^{-3} (4.45×10^{-3}) WST: 9.81×10^{-3} (9.82×10^{-3}) SKAT: 0.0655 (0.0655)
		12:132322812:C:A	4.74E-03	0.0828				
		12:132323249:G:A	1.41E-05	0.6916				
		12:132323250:C:G (rs4964883)	0.0178	0.0017				
		12:132325122:C:T	1.57E-04	0.0116				
		12:132325135:G:A	2.01E-03	0.4579				
		12:132325155:G:A	4.95E-05	0.1567				

		12:132325204:T:G	2.13E-04	0.2598				
		12:132326297:C:T	1.68E-04	0.1078				
		12:132328566:C:T	2.95E-04	0.2026				
		12:132334379:G:A	3.19E-04	0.7728				
		12:132334403:G:A	8.98E-05	0.4139				
		12:132334430:G:A	5.99E-04	0.9678				
		12:132334460:A:G	3.68E-03	0.0332				
		12:132335602:T:C	8.47E-05	0.9274				
		12:132335664:C:T	9.59E-04	0.9049				
		12:132335685:G:A	5.02E-03	0.4770				
PY	*CHRNA2*	8:27320526:G:T	4.96E-03	0.0399	Burden: 6.40×10^{-4} WST: 0.19 SKAT: 0.0026 [+]	Burden: 0.043 WST: 0.75 SKAT: 0.041	rs56229264	Burden: 0.04 (0.04) WST: 0.73 (0.73) SKAT: 0.038 (0.038)
		8:27320528:C:T	8.42E-05	0.5917				
		8:27320726:C:T	4.31E-04	0.6571				
		8:27321189:G:A (rs56229264)	0.01606	0.0063				
		8:27324812:C:T	6.47E-05	0.5914				
		8:27327391:G:A	7.86E-06	0.0293				
		8:27327432:G:A	5.94E-04	0.1764				

Supp. Table 7: Results from Mendelian Randomization (MR) analyses to assess causal effects of smoking on BMI, schizophrenia, and education attainment. Three complementary approaches were performed including i) MR-Egger, ii) weighted median iii) inverse variance weighted regression. The analyses were performed using the R package Mr Base using MR-Base ID: 2 for BMI, MR-Base ID: 22 for schizophrenia and MR-Base ID: 1001 for educational attainment. We also performed sensitivity analyses to check for reverse causality.

A. Smoking Initiation (SI) with BMI, schizophrenia, and education attainment using smoking initiation associated SNVs as instrumental variables (IVs). The *P*-value for the intercept for MR-Egger is provided in parentheses.

MR Method	Number of IVs	Beta (SE)	*P*-VALUE
SI → BMI			
MR Egger	43	-0.31 (0.12)	0.013 (0.001)
Weighted median	43	-0.043 (0.033)	0.19
Inverse variance weighted	43	0.061 (0.065)	0.35
SI → Schizophrenia			
MR Egger	46	0.199 (0.32)	0.54 (0.57)
Weighted median	46	0.083 (0.099)	0.403
Inverse variance weighted	46	0.36 (0.15)	0.014
SI -> Education Attainment			
MR Egger	47	-0.075 (0.06)	0.202(0.39)
Weighted median	47	-0.087 (0.02)	3.20e-5
Inverse variance weighted	47	-0.120 (0.03)	1.62e-6

B. Assessment of potential reverse causation on Smoking Initiation (SI) induced by BMI, schizophrenia, and education attainment using BMI, schizophrenia, and education attainment associated SNVs as instrumental variables (IVs)

MR Method	Number of IVs	Beta (SE)	*P*-VALUE
BMI→ SI			
MR Egger	60	0.022 (0.023)	0.34 (0.81)
Weighted median	60	0.024 (0.018)	0.17
Inverse variance weighted	60	0.018 (0.015)	0.23
Schizophrenia → SI			
MR Egger	8	0.196 (0.13)	0.19 (0.13)
Weighted median	8	0.00038 (0.025)	0.99
Inverse variance weighted	8	-0.027 (0.028)	0.33
Education Attainment → SI			
MR Egger	10	-0.81 (0.76)	0.32 (0.99)
Weighted median	10	-0.13 (0.09)	0.16
Inverse variance weighted	10	-0.27 (0.16)	0.088

C. Assessment of potential causal effect of Cigarettes per day (CPD) on body mass index (BMI), schizophrenia, and education attainment using cigarettes per day associated SNPs as instrumental variables

MR Method	Number of IVs	Beta(SE)	*P*-VALUE
CPD → BMI			
MR Egger	9	-0.18 (0.062)	0.021 (0.033)
Weighted median	9	-0.087 (0.033)	0.0088
Inverse variance weighted	9	-0.051 (0.048)	0.29
CPD → Schizophrenia			
MR Egger	12	0.49 (0.29)	0.12 (0.044)
Weighted median	12	0.44 (0.13)	0.00095
Inverse variance weighted	12	0.31 (0.17)	0.068
CPD → Education Attainment			
MR Egger	11	0.035 (0.044)	0.45 (0.041)
Weighted median	11	-0.041 (0.022)	0.066
Inverse variance weighted	11	-0.049 (0.031)	0.11

D. Assessment of potential reverse causation on CPD induced by BMI, schizophrenia, and education attainment using BMI, schizophrenia, and education attainment associated SNVs as instrumental variables (IVs)

MR Method	Number of IVs	Beta (SE)	*P*-VALUE
BMI → CPD			
MR Egger	60	0.015 (0.047)	0.74 (0.47)
Weighted median	60	0.061 (0.041)	0.14
Inverse variance weighted	60	0.043 (0.028)	0.13
BMI → Schizophrenia			
MR Egger	8	0.303 (0.72)	0.69 (0.96)
Weighted median	8	-0.0099 (0.05)	0.85
Inverse variance weighted	8	0.26 (0.16)	0.11
Education Attainment → CPD			
MR Egger	8	-1.12 (0.77)	0.19 (0.28)
Weighted median	8	-0.079 (0.28)	0.78
Inverse variance weighted	8	-0.246 (0.209)	0.24

Supp. Table 8: Evaluation of potential collider bias in UK Biobank (UKBB) analyses. We performed two sensitivity analyses to understand whether collider bias influenced our results: i) performing meta-analysis without UK BiLEVE, the component of the UK Biobank that is enriched heavy smokers, ii) performing UK Biobank analysis without adjusting for genotyping array. We compared these results with our meta-analysis which adjusted for UK BiLEVE and UK Biobank Axiom arrays. The magnitude of the genetic effect estimates are very comparable for the three analyses, including the results with and without the UK BiLEVE samples. We used CPD as the outcome.

rsID (Exome-chip ID)	**Chr:Position (REF/ALT)**	**Meta-analysis including UK BiLEVE**		**Meta-analysis without UK BiLEVE**		**UKBB without adjustment for array**
		Beta (SE)	***P*-VALUE**	**Beta (SE)**	***P*-VALUE**	**Beta (SE)**
rs141611945 (exm118559)	1:161771868 (A/G)	1.7 (0.33)	2.95×10^{-7}	1.7 (0.33)	6.1×10^{-7}	1.2 (0.46)
rs1190736 (exm1659559)	X:136113464 (C/A)	-0.028 (0.0055)	3.45×10^{-7}	-0.016 (0.0045)	$3.2x10^{-4}$	-0.019 (0.0034)
rs2960306 (exm383568)	4:2990499 (G/T)	-0.017 (0.0041)	4.33×10^{-5}	-0.012 (0.0045)	$5.3x10^{-3}$	-0.017 (0.0044)
rs8102683	19:41363765	0.062 (0.0076)	4.5×10^{-16}	0.055 (0.010)	8.6×10^{-8}	0.044 (0.0031)
rs28399442	19:41354458 (C/A)	-0.18 (0.025)	2.3×10^{-12}	-0.18 (0.035)	2.7×10^{-7}	-0.17 (0.014)
rs3865453	19:41338556 (C/T)	-0.078 (0.014)	3.0×10^{-8}	-0.074 (0.019)	1.1×10^{-4}	-0.068 (0.0083)
rs938682	15:78882925 (G/A)	0.094 (0.0043)	8.8×10^{-108}	0.099 (0.0046)	1.6×10^{-100}	0.085 (0.0044)

Individual study descriptions

This section describes study-specific characteristics. All participants provided written informed consent and studies were approved by local Research Ethics Committees and/or Institutional Review boards.

Airwave (Airwave Health Monitoring Study) is a large-scale cohort of police employees. Study details are given elsewhere[14].

ASCOT (Anglo Scandinavian Cardiac Outcomes Trial) is a prospective, randomized, open, blinded endpoint trial for which details are given elsewhere[15].

Details of the **1958BC** (**British 1958 Birth Cohort)** study have been previously reported[16].

BRIGHT (The British Genetics of Hypertension) study is a hypertension case-control study. Study details are given elsewhere[17].

The CROATIA study was initiated to investigate the use of isolated rather than urban populations for the identification of genes associated with medically-relevant quantitative traits. Three cohorts have been recruited as part of the CROATIA study, of which one, **CROATIA-Korcula**[18] has been used in these analyses. CROATIA-Korcula was recruited from 2007 to 2008 from the town of Korcula and the villages of Lumbarda, Zrnovo and Racisce on the island of Korcula, Croatia with 969 adults aged 18-98 agreeing to participate. Participants donated blood for DNA extraction and biochemical measurements as well as undergoing some anthropometric measurements and physiological tests to measure traits such as height, weight and blood pressure, and finally completing several questionnaires relating to general health, medical history, diet and lifestyle. Ethical approval was obtained from appropriate regulatory bodies in both Scotland and Croatia and participants gave informed consent prior to joining the study.

The **DIABNORD**, **FIA3 (FörstagångsInsjuknande i hjärtinfarkt i AC-län 3; English: First myocardial Infarction in AC county 3)** and **GLACIER (The Gene-Lifestyle interactions And Complex traits Involved in Elevated disease Risk)** studies are nested within the Västerbotten Health Survey, which are part of the Northern Sweden Health and Disease Study, a population-based prospective cohort study from northern Sweden. Study details are given elsewhere[19].

EFSOCH (The Exeter Family Study of Childhood Health) is a prospective study of parents and children from a consecutive birth cohort. Study details are given elsewhere[20].

EGCUT (Estonian Genome Project of University of Tartu) is a population-based biobank of the Estonian Genome Project of University of Tartu. The project is conducted according to the Estonian Gene Research Act and all participants have signed the broad informed consent (www.biobank.ee). In total, 52,000 individuals aged 18 years or older participated in this cohort (33% men, 67% women). The population distributions of the cohort reflect those of the Estonian population (83% Estonians, 14% Russians and 3% other). General practitioners (GP) and physicians in the hospitals randomly recruited the participants and a PC assisted interview was conducted for 1–2 hours. Data on demographics, genealogy, educational and occupational history, lifestyle and anthropometric and physiological data were assessed. Study details are given elsewhere (as Estonian Biobank)[21].

EMBRACE (Epidemiological Study of Familial Breast Cancer) aims to "obtain prospective estimates of cancer incidence in BRCA1/2 mutation carriers; determine lifestyle factors which may modify cancer risk; study modifying genes; examine efficacy of interventions (mastectomy, oophorectomy etc) and provide a basis for future intervention trials". Study details can be found at ccge.medschl.cam.ac.uk/embrace.

Fenland (Fenland Study) is a population-based cohort study designed to investigate the association between genetic and lifestyle environmental factors and the risk of obesity, insulin sensitivity, hyperglycemia and related metabolic traits in men and women aged 30 to 55 yrs. Volunteers were recruited from General Practice sampling frames in the Fenland, Ely and Cambridge areas of the Cambridgeshire Primary Care Trust in the U.K.

The **Generation Scotland: Scottish Family Health Study** (**GS:SFHS**) is a collaboration between the Scottish Universities and the NHS, funded by the Chief Scientist Office of the Scottish Government. GS:SFHS is a family-based genetic epidemiology cohort with DNA, other biological samples (serum, urine and cryopreserved whole blood) and socio-demographic and clinical data from ~24,000 volunteers, aged 18-98 years, in ~7,000 family groups. Participants were recruited across Scotland, with some family members from further afield, from 2006-2011. Most (87%) participants were born in Scotland and 96% in the UK or Ireland. The cohort profile has been published[22]. GS:SFHS operates under appropriate ethical approvals, and all participants gave written informed consent. Generation Scotland is a collaboration between the University Medical Schools and National Health Service in Aberdeen, Dundee, Edinburgh and Glasgow (UK).

GoDARTS (Genetics of Diabetes Audit and Research Tayside) study recruits diabetic patients and non-diabetic matched controls in Tayside, Scotland; and details can be found elsewhere and at diabetesgenetics.dundee.ac.uk**.**

The KORA studies (Cooperative Health Research in the Region of Augsburg; German: Kooperative Gesundheitsforschung in der Region Augsburg) are a series of independent population based studies from the general population living in the region of Augsburg, Southern Germany[23]. **KORA F4** including 3,080 individuals was conducted from 2006-2008 as a follow-up study to KORA S4 (1999-2001).

The **Lothian Birth Cohort 1921 (LBC1921)** consists of 550 (234 male) relatively healthy individuals, assessed on cognitive and medical traits at a mean age of 79.1 years (SD = 0.6). They were born in 1921, most took part in the Scottish Mental Survey of 1932, and almost all lived independently in the Lothian region (Edinburgh City and surrounding area) of Scotland. A full description of participant recruitment and testing can be found elsewhere[24]. Genotyping was performed at the Wellcome Trust Clinical Research Facility, Edinburgh. Quality control measures were applied and 517 participants remained.

The **Lothian Birth Cohort 1936 (LBC1936)** consists of 1,091 relatively healthy individuals assessed on cognitive and medical traits at about 70 years of age. They were all born in 1936 and most took part in the Scottish Mental Survey of 1947. At baseline the sample of 548 men and 543 women had a mean age 69.6 years (s.d. = 0.8). They were all Caucasian, community-dwelling, and almost all lived in the Lothian region (Edinburgh city and surrounding area) of Scotland. A full description of participant recruitment and testing can be found elsewhere[24]. Genotyping was performed at the Wellcome Trust Clinical Research Facility, Edinburgh. Quality control measures were applied and 1,005 participants remained.

LifeLines is a multi-disciplinary prospective population-based cohort study examining in a unique three-generation design the health and health-related behaviours of 165,000 persons living in the North East region of The Netherlands. Study details can be found elsewhere[25].

LOLIPOP (London Life Sciences Prospective Population Study) is a population based cohort study of ~30,000 South Asian and European white men and women, aged 35-75 years, recruited from the lists of 58 General Practitioners in West London, UK. Study details are given elsewhere[26].

LRGP (Leidsche Rijn GezondheidsProject) cohort is a population-based cohort that includes over 10,000 residents of Leidsche Rijn (Utrecht, the Netherlands). Study details are given elsewhere[27]**.**

OxBB (Oxford BioBank) is a “collection of 30-50 year old healthy men and women living in Oxfordshire”. Study details can be found elsewhere[28] and at www.oxfordbiobank.org.uk.

SEARCH (**Studies of Epidemiology and Risk factors in Cancer Heredity)** is a population-based study with cases ascertained through the Eastern Cancer Registration and Information Centre (http://www.ecric.org.uk). Study details can be found at ccge.medschl.cam.ac.uk/search-study.

The **Study of Health in West Pomerania (SHIP)** is a cross-sectional, population based survey in a region in the Northeast of Germany. Study details are given elsewhere[29].

SIBS (Sisters in Breast Screening) uses families identified through the breast screening program in the United Kingdom; and study details are given elsewhere[30].

The **United Kingdom Household Longitudinal Study (UKHLS)**, also known as Understanding Society (https://www.understandingsociety.ac.uk) is a longitudinal panel survey of 40,000 UK households (England, Scotland, Wales and Northern Ireland) representative of the UK population. Participants are surveyed annually since 2009 and contribute information relating to their socioeconomic circumstances, attitudes, and behaviours via a computer assisted interview. The study includes phenotypical data for a representative sample of participants for a wide range of social and economic indicators as well as a biological sample collection encompassing biometric, physiological, biochemical, and haematological measurements and self-reported medical history and medication use. The United Kingdom Household Longitudinal Study has been approved by the University of Essex Ethics Committee and informed consent was obtained from every participant.

For a subset of individuals who took part in a nurse health assessment, blood samples were taken and genomic DNA extracted. Of these, 10,484 samples were genotyped at the Wellcome Trust Sanger Institute using the Illumina Infinium HumanCoreExome-12 v1.0BeadChip.

Atherosclerosis Risk in Communities (ARIC), is designed to look at risks and clinical outcomes associated with atherosclerosis in older population. To date, the study has collected information in approximately 4000 people aged 45-64 years old. Details can be on www2.cscc.unc.edu/aric.

Collaborative Study on the Genetics of Alcoholism (COGA), is a collaborative effort by the NIAAA to study the genetic effects on alcoholism. They have data on 2,255 extended families from six sites (SUNY Downstate Health Sciences Center, University of Connecticut, Indiana University, Washington University, University of Iowa, and The University of California at San Diego). Details can be on www.niaaa.nih.gov/research/major-initiatives/collaborative-studies-genetics-alcoholism-coga-study.

Finnish Twin Cohort (FTC) nation-wide population-based twin family study in Finland. It follows a series of cohort of twins in three stages stages, with twins born before 1958 (started in 1974), twins born 1975-1979 (started in 1991) and twins born 1983-1987 (starting from 1974, 1987 and started in 1994)1995.. Currently, there are 25,932 individuals in the study. Details can be found on www.twinstudy.helsinki.fi and reference[31].

Finland-United States Investigation of NIDDM Genetics (FUSION) attempts to identify genetic risk for type 2 diabetes mellitus using a case-control sample. More study information can be found here: fusion.sph.umich.edu/Pubs/papers/zeggini_diagram_t2dmeta_2008.pdf.

Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO) studies colorectal cancer in a case-control study using data from over 40,000 participants.

Genes for Good Facebook study (GFG) is an application-based study started from the University of Michigan that uses Facebook as a platform to communicate with participants.

The **Health and Retirement Study (HRS)** is a longitudinal survey of a representative sample of Americans over the age of 50. The current sample is over 26,000 persons in 17,000 households. The study interviews respondents every two years about income and wealth, health and use of health services, work and retirement, and family connections. DNA was extracted from saliva collected during a face-to-face interview in the respondents' homes. These data represent respondents who provided DNA samples and signed consent forms in 2006, 2008, and 2010. Details can be found in reference[32].

ID1000 is a study in Netherlands where 1000 young adults participated in MRI studies at the Spinoza Center for Neuroimaging, in the Amsterdam Brain & Cognition research center.

Multi-ethnic Cohort Study (MEC) is an ethnically diverse cohort study based in Hawaii and California in the US that looks at the genetic risk that influences Cancer.

METabolic Syndrome In Men (METSIM) looks at risk of type 2 diabetes (T2D), cardiovascular disease (CVD), and insulin resistance in men aged from 45 to 73 years in eastern Finland.

Montreal Heart Institute (MHI) is a large hospital cohort based in Montreal studying cardiovascular diseases and its genetic risk factors.

NAG-OZALC is a study of alcohol disorders in a multi-cohort Australian twin-family sample. NIDA Nicotine Addiction Genetics [NAG] project is one of 3 coordinated studies that works with the OZALC data by identifying and working with the heavy smokers in the sample.

Netherlands study of Cognition, Environment and Genes (NESCOG) is a national representative sample of adults in Netherlands that investigates the underlying genetic factors related to intelligence.

sardiNIA is a study of longevity on a sample from Sardinia focused on the use of founder populations to simplify analysis of complex traits.

TwinsUK: A study of adult twins to study the genetic and environmental effects on age-related diseases and complex traits.

The **UK BiLEVE** samples comprised of 48,930 individuals selected for the UK Biobank Lung Exome Variant Evaluation (UK BiLEVE) project[12]. **UK Biobank** (http://www.ukbiobank.ac.uk/) contains data from 502,682 individuals including UK BiLEVE (94% of self-reported European ancestry) with extensive health and lifestyle questionnaire data, physical measures and DNA[33].

Women's Health Initiative (WHI) is a complex study that is designed with clinical trials and observational cohorts in order to look at the risk factors in aging women.

The Copenhagen Ischaemic Heart Disease Study (CIHDS) study is comprised of cases with myocardial infarction and other major acute coronary syndromes. The cases were recruited from Copenhagen University Hospital during the period from 1991 to 2009. In addition to a diagnosis of acute coronary syndrome, these cases also had stenosis or atherosclerosis on coronary angiography and/or positive results on exercise electrocardiography. Cases were classified by World Health Organization International Classification of Diseases-Eighth Revision, codes 410 to 414; International Classification of Diseases-Tenth Revision, codes I20 to I25, and through review of all hospital admissions and diagnoses entered in the national Danish Patient Registry and all causes of death entered in the national Danish Causes of Death Registry, as previously described[34].

The Copenhagen General Population Study (CGPS) is a population-based prospective study initiated in 2003 with ongoing enrolment[34]. Participants were selected on the basis of the national Danish Civil Registration System to reflect the adult Danish population age 20 to ≥80 years. Data were obtained from a questionnaire, a physical examination, and blood samples including deoxyribonucleic acid extraction. Follow-up was 100% complete; that is, no participant was lost to follow-up.

Copenhagen City Heart Study (CCHS) is a population-based prospective study initiated in 1976 with follow-up examinations from 1981 to 1983, 1991 to 1994, and 2001 to 2003[35]. Selection of individuals for the CCHS was based on the same criteria as for the CGPS. Information on diagnosis of CAD (defined as WHO ICD 8 410 to 414 and WHO-ICD 10 I20 to I25) was collected and verified from 1976 until 2010 by reviewing all hospital admissions and diagnoses entered in the national Danish Patient Registry, and by reviewing all causes of death entered in the national Danish Causes of Death Registry[35, 36]. Again, follow-up was 100% complete for both non-fatal coronary outcomes and mortality.

European Investigation into Cancer and Nutrition-CVD (EPIC-CVD): EPIC is a multi-centre prospective cohort study[37] of 519,978 participants (366,521 women and 153,457 men, mostly aged 35–70 years) recruited between 1992 and 2000 in 23 centres located in 10 European countries. Participants were invited mainly from population-based registers (Denmark, Germany, certain Italian centres, the Netherlands, Norway, Sweden, UK)[38]. Other sampling frameworks included: blood donors (Spain and Turin and Ragusa in Italy); screening clinic attendees (Florence in Italy and Utrecht in the Netherlands); people in health insurance programmes (France); and health conscious individuals (Oxford, UK)[38]. About 97% of the participants were of white European ancestry. Prevalent CAD was ascertained through self-reported history of MI or angina, or registry-ascertained CAD event prior to baseline. EPIC-CVD employs a nested case-cohort design, analogous to the EPIC-InterAct study for type-2 diabetes[39] which established a common set of referents through selection of a random sample of the entire cohort ("subcohort"). Incident CAD cases have been defined as fatal and non-fatal MI and other major acute coronary events, according to ICD-10 codes I20-I25. All centres have recorded cause-specific mortality through mortality registries and/or active follow-up, and have ascertained and validated incident fatal and non-fatal CAD through a combination of methods (eg, morbidity registers, general practice records, MONICA registries, self-report, clinical records[39]).

Bangladesh Risk of Acute Vascular Events (BRAVE) is a retrospective case-control study of first-ever confirmed acute myocardial infarction (MI) in Bangladesh. Patients (male or female; age between 30-80 years) admitted to the emergency rooms of the collaborating hospital in Dhaka, Bangladesh were eligible for inclusion as MI cases if they fulfilled all of the following criteria: i) presented within 24 hours of the onset of sustained clinical symptoms suggestive of MI lasting longer than 20 minutes, including chest pain and breathlessness; ii) had ECG changes indicative of MI (new pathologic Q waves, at least 1 mm ST elevation in any 2 or more contiguous limb leads or a new left bundle branch block, or new persistent ST-T wave changes diagnostic of a non-Q wave MI) with a subsequent confirmation by troponin-I measurements; and iii) had no previous cardiovascular diseases; defined as self-reported history of angina, MI, coronary revascularisation, transient ischaemic attack, stroke or evidence of CAD on prior ECG or in other medical records. Participants were not recruited into BRAVE if any of the following features had been evident: i) a previous history of cardiovascular disease (including self-reported MI, angina, coronary revascularization, stroke, transient ischaemic attack, or peripheral vascular disease, and, in cases, presence of cardiogenic shock); ii) a history of a viral or bacterial infection in the previous 2 weeks; iii) current hospitalization for acute cerebrovascular events; iv) MI secondary to any surgery; v) documented chronic conditions, such as malignancy, any chronic infection, leprosy, malaria or other bacterial/parasitic infections, chronic inflammatory disorders, hepatitis or renal failure on past medical history; vi) pregnancy or related conditions; or vii) unable to provide consent. Controls were hospital based and frequency-matched to cases on age (within 5 year age bands) and sex, and without a self-reported history of cardiovascular disease.

Pakistan Risk of Myocardial Infarction Study (PROMIS) is an ongoing retrospective case-control study of first-ever confirmed acute MI in Pakistan. Since 2005, the study has enrolled close to 18,500 MI cases and equivalent number of controls; the present investigation has included all MI cases and controls that had been enrolled until 2011. Patients aged 30-80 years who were admitted to the emergency rooms of nine recruitment centres across Pakistan[40] were eligible for inclusion as cases if they fulfilled all of the following criteria: symptoms within 24 hours of hospital presentation; typical ECG changes; and positive troponin-I test. To identify referents from approximately the same source population as the cases, controls were identified contemporaneously in the same hospitals as the index cases and selected from among people who had no history of CVD and who were: visitors of patients attending the outpatient department; patients attending outpatient departments for routine non-cardiac complaints; or non-blood relatives visiting index MI cases. Controls were frequency-matched to MI cases by sex and age (5-year bands). People with recent illnesses or infections were not eligible.

MONICA Risk Genetics, Archiving and Monograph (**MORGAM**) is a consortium of cohort studies on cardiovascular diseases, whose data have been harmonized into one database for joint analysis[41]. For the current analysis, the following cohorts were included: Brianza cohorts 01, 02 and 03 (Italy); the placebo cohort of the ATBC Study (Finland); FINRISK cohort 1992 and 1997 (Finland); Lille, Strasbourg and Toulouse cohorts of the PRIME study (France); Augsburg (KORA) cohorts S1, S2 and S3 (Germany); and Belfast cohort of the PRIME study (Northern Ireland) . The cohorts were based on random population samples, except ATBC which included only smokers, and they were recruited between years 1984 and 1997. For genetic analyses, a case-cohort design was used.

The **INTERVAL** study comprised about 50,000 participants nested within a randomised trial of varying blood donation intervals46. Between mid-2012 and mid-2014, whole-blood donors aged 18 years and older were consented and recruited at 25 centers of England's National Health Service Blood and Transplant (NHSBT). Participants completed an online questionnaire including questions about demographic characteristics (e.g., age, sex, ethnic group), anthropometry (height, weight), lifestyle (e.g., alcohol and tobacco consumption) and diet. Participants were generally in good health because blood donation criteria exclude people with a history of major diseases (such as myocardial infarction, stroke, cancer, HIV, and hepatitis B or C) and those who have had recent illness or infection

Study-level Quality Control Procedures

Consortium for the Genetics of Smoking Behaviour (CGSB)

For AIRWAVE, ASCOT, 1958BC, BRIGHT, DIABNORD, EFSOCH, EGCUT, EMBRACE, FENLAND, FIA3, GLACIER, GoDARTS, KORA F4, LifeLines, LOLIPOP, LRGP, OXBB, SEARCH, SHIP, SIBS, genotype calling and quality control were carried out in accordance with the Exome-chip Quality Control SOP Version 5 (20/11/2012), as developed within the UK exome-chip consortium (by Mahajan, A., Robertson, N. and Rayner, W). Genotypes were initially called using Gencall in Illumina's Genome Studio software (Illumina Inc. Illumina GenCall Data Analysis Software, 2005). Quality control of SNPs and samples was subsequently performed at study level. Initial filters applied excluded SNPs with very low call rate (<90%) and samples with low call rate, heterozygosity outliers, duplicates, gender mismatches and ancestral outliers. SNPs with missing data were then recalled using genotype calling software zCall[42]. All alleles were mapped to the forward strand of human genome build 37 and secondary exclusions were applied to remove SNPs with low call rate (<99%) or deviations from Hardy Weinberg Equilibrium ($P<10^{-4}$). Samples with call rate <99% and heterozygosity outliers were also excluded.

For GS:SFHS, CROATIA-Korcula and LBC1936, LBC1921 , genotypes were called using Gencall in Illumina's Genome Studio software (https://www.illumina.com/Documents/products/technotes/technote_gencall_data_analysis_software.pdf) via the CHARGE Consortium joint calling cluster file (http://www.chargeconsortium.com/main/exomechip) and quality control of the genotype data was undertaken according to the CHARGE exome chip best practices, described elsewhere[43].

UKHLS: Genotype calling was performed using the Illumina GenCall software. Sample-level quality control (QC) was performed using the following filters: call rate <98%, autosomal heterozygosity outliers (>3 SD), gender mismatches, duplicates as established by identity by descent (IBD) analysis (PI_HAT >0.9), ethnic outliers as determined by combining with 1000 Genomes Project data and carrying out IBD followed by multidimensional scaling. In total, 9,965 samples passed QC. Variant-level QC was performed as follows: variants were mapped to forward strand of human genome build 37. Variants with Hardy-Weinberg equilibrium $P < 1\times10^{-4}$, a call rate < 98% and poor genotype clustering values (< 0.4) were removed, as well as Y-chromosome and mitochondrial variants.

GSCAN

Study-level QC procedures and analysis plan for the GSCAN participating cohorts can be found at: http://gscan.sph.umich.edu/exome/analysis_plan.

INTERVAL

The genotyping protocol and QC for the INTERVAL samples (n~50,000) have been described previously in detail[44]. Briefly, DNA extracted from buffy coat was used to assay approximately 830,000 variants on the Affymetrix Axiom UK Biobank genotyping array at Affymetrix (Santa Clara, California, US). Genotyping was performed in multiple batches of approximately 4,800 samples each. Sample QC was performed including exclusions for sex mismatches, low call rates, duplicate samples, extreme heterozygosity and non-European descent. An additional exclusion made for this study was of one participant from each pair of close (first- or second-degree) relatives, defined as $\hat{\pi}>0.187$. Identity-by-descent was estimated using a subset of variants with a call rate >99% and MAF >0.05 in the merged dataset of both subcohorts, pruned for linkage disequilibrium (LD) using PLINK v1.9. Multi-dimensional scaling was performed using PLINK v1.9 to create components to account for ancestry in genetic analyses.

Prior to imputation, additional variant filtering steps were performed to establish a high-quality imputation scaffold. In summary, 654,966 high quality variants (autosomal, non-monomorphic, bi-allelic variants with Hardy Weinberg Equilibrium (HWE) $P>5\times10^{-6}$, with a call rate of >99% across the INTERVAL genotyping batches in which a variant passed QC, and a global call rate of >75% across all INTERVAL genotyping batches) were used for imputation. Variants were phased using SHAPEIT3 and imputed using a combined 1000 Genomes Phase 3-UK10K reference panel. Imputation was performed via the Sanger Imputation Server (https://imputation.sanger.ac.uk) resulting in 87,696,888 imputed variants.

CHD Exome+ Consortium

The CHD Exome + consortium is composed of 8 different cohorts, 6 from Europe (EPIC-CVD, CCHS, CGPS, CIHDS, PROSPER, MORGAM) and 2 from South Asia (BRAVE, PROMIS). The three Copenhagen collections (CCHS, CIHDS, CGPS) were genotyped in Copenhagen, all other genotyping was performed in Cambridge, UK. Two versions of the Exome+ chip were used (both with the same standard Exome chip content but different custom content) necessitating some collections to be genotyped in batches (CIHDS, CGPS, PROMIS, BRAVE). Consequently, genotype calling was done at the batch level, with all batches going through the same calling and QC pipeline in Cambridge. EPIC-CVD and CCHS were only genotyped on version 1 of the chip, while PROSPER, were only genotyped on version 2 of the chip and hence were genotyped as single batches. Details of the consortium design are summarised in the table below.

Ethnicity	Collection	Study design	Number of genotyping batches	Association Study
South Asian	BRAVE	Case-control	2	BRAVE
	PROMIS	Case-control	3*	PROMIS
European	EPIC-CVD	Case-cohort	1	EPIC
	CCHS	Prospective	1	CCHS
	CGPS	Cross-sectional	2	CGPS
	CIHDS	Case series	2	CIHDS
	MORGAM	Case-cohort	1	MORGAM
	PROSPER	Nested case-control within trial	1	PROSPER
Total number	**8**	**-**	**13**	**8**

* Note, PROMIS was genotyped on 'version 1' of the chip and in two batches on 'version 2' of the chip, as samples were still being recruited while genotyping was being undertaken.

QC steps were undertaken at both the batch and study level as follows:

<u>Genotype batch-level QC:</u>

- Sample exclusions based on pre-genotype calling
  - o raw intensities pre-calling (poor performing plates/arrays/sample intensity outliers)
- Sample exclusions post genotype calling
  - o heterozygosity (samples +/-3SD from batch mean heterozygosity)
  - o call rate (samples more than 3SD less than batch mean, equates to ~0.97)
  - o sex mismatches or genotype discordance with previous arrays
- SNV exclusions based on:
  - o call rate (SNVs with call rate <0.97 in CHD cases or controls)
  - o HWE ($Z^2 > 24$ [equivalent to $P<1x10^{-06}$] for common SNVs [MAF ≥ 5%], $Z^2 > 64$ [equivalent to $P<1x10^{-15}$] for rare SNVs [MAF<5%] in controls or all samples in genotyping batch)
  - o Variants failing visual cluster plot inspections.

<u>Study-level QC:</u>

- Sample exclusions based on:
  - o Ancestry outliers from PCA
  - o Duplicates identified from kinship
- SNV exclusions based on:

- HWE in controls or all samples in study ($Z^2 > 24$ [equivalent to $P<1x10^{-06}$] for common SNVs [MAF ≥ 5%], $Z^2 > 64$ [equivalent to $P<1x10^{-15}$] for rare SNVs [MAF<5%])

UK Biobank Phenotype Information

Cigarettes per day (CPD): We defined CPD using the combination of phenotype codes of 2887 (number of cigarettes previously smoked daily), 3456 (number of cigarettes currently smoked daily), and 6183 (number of cigarettes previously smoked daily (current cigar/pipe smokers)). Extreme outliers with values >60 were removed. The phenotype was binned and recoded according to 1-10-> 1, 11-20-> 2, 21-30-> 3, >30-> 4.

Smoking Initiation: We coded the ever-regular cigarette smoker as 2 and the individuals that were never a regular cigarette smoker as 1.

We defined an individual as ever-regular smokers if:

1) They answered the field 2644 (light smokers, at least 100 smokes in lifetime) as “Yes”; or
2) They responded "Hand-rolled cigarettes" or "Manufactured cigarettes" to 2877 (type of tobacco previously smoked); or
3) They were former cigarette smokers but currently use a different tobacco product, as indicated by a non-null response to 6183; or
4) They responded "Hand-rolled cigarettes" or "Manufactured cigarettes" to 3446 (Type of tobacco currently smoked).

The individuals that were deemed a never regular smoker if:

1) They answered “No” to 2644; or
2) They responded "I have never smoked" to 1249 (past tobacco smoking).

Pack-Years: For current smokers, the number of years of smoking was defined as difference between 21003 (age when attended assessment centre) and 3436 (age started smoking in current smokers). For previous smokers, the number of years of smoking was defined by the difference between 2897 (age stopped smoking) and 2867 (age started smoking in former smokers). The number of years of smoking that was less than one (1) was set to missing. Pack-years was then calculated as the non-binned CPD, divided by 20, times the number of years of smoking. The numbers were log transformed to reduce the impact of potential outliers.

Smoking Cessation: we coded current smoker as ‘2’, and former smoker as ‘1’. Specifically, we defined an individual as a former smoker if:

1) They answered yes to 2644; or
2) They responded "Hand-rolled cigarettes" or "Manufactured cigarettes" to 2877.

We define an individual to be a current smoker if they answered "Hand-rolled cigarettes" or "Manufactured cigarettes" to 3446.

Phenotypic Variance Explained

We estimated the proportion of variance explained by the set of all conditionally independently associated variants (**Tables 1-3** and **Suppl. Table 3**). The joint effects of variants in a locus were approximated by

$\hat{\vec{\beta}}_{JOINT} = \mathbf{V}_{\mathbf{META}}^{-1}\vec{U}_{META}$, where $\vec{U}_{META}$ is the single variant score statistics and $\mathbf{V}_{\mathbf{META}}$ is the covariance matrix between them. The phenotypic variance explained by the independently associated variants in a locus is given by $\hat{\vec{\beta}}_{joint}^{T}\mathrm{cov(G)}\hat{\vec{\beta}}_{JOINT}$, where cov(G) is the partial covariance between different variants as estimated from $\mathbf{V}_{\mathbf{META}}$. Together the phenotypic variance explained by the novel variants were 0.53% (SI), 0.0026% (PY), 0.72% (CPD) and 0.016% (SC). The phenotypic variance explained by both novel and known variants were 0.61% (SI), 0.31% (PY), 1.2% (CPD), and 0.027% (SC). Our novel variants substantially improved the phenotypic variance explained, yet the total phenotypic variance explained remained low for smoking related traits.

Genes of interest

Interestingly, some of the associated variants appear to have regulatory roles on nicotine addiction related genes. For example, rs11776293 (an intronic variant in *EPHX2*; **Table 2**), was an eQTL for *CHRNA2*, with the T allele increasing the gene's expression in brain cerebellum in GTEx (*P*=2.5x10^{-5}; β=0.61). *CHRNA2*, a gene that showed nominal association with pack-years in our gene-based tests (**Suppl. Table 6**), encodes the α2 subunit nicotinic acetylcholine receptor gene. *CHRNA2* has previously been reported with nominal evidence of association with common SNVs in small candidate gene studies[45, 46]. We also identified an association of *CHRNA2* with pack-years in the gene-based tests, although this was mostly driven by a single variant, rs56229264. Common variants at this locus have been shown to be associated with lung cancer and cannabis use disorder[47], and potentially regulating the expression of *CHRNA2* in the cerebellum.[48]

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