SUPPLEMENTAL MATERIAL

Supplemental Table 1. Coronary Heart Disease Associated Single Nucleotide Polymorphisms Included in the Polygenic Risk Score

Lead SNP	Proxy SNP (r^2)	Gene	Risk Allele	Other Allele	Risk Allele Frequency	Risk Estimate (published)	Reference	Pleiotropy*
rs599839	rs646776 (0.91)	SORT1	T	C	0.77	1.11	CARDIoGRAM[1]	Lipids, Type 2 Diabetes
rs17114036		PPAP2B	A	G	0.92	1.11	CARDIoGRAMplusC4D[2]	Blood Pressure
rs11206510		PCSK9	T	C	0.82	1.08	CARDIoGRAM[1]	Lipids
rs17465637		MIA3	C	A	0.74	1.14	CARDIoGRAM[1]	
rs6725887		WDR12	G	A	0.13	1.12	CARDIoGRAMplusC4D[2]	Lipids
rs9818870		MRAS	T	C	0.16	1.07	CARDIoGRAMplusC4D[2]	
rs17609940		ANKS1A	G	C	0.79	1.07	CARDIoGRAM[1]	
rs12526453		PHACTR1	G	C	0.67	1.1	CARDIoGRAM[1]	
rs12190287		TCF21	C	G	0.63	1.07	CARDIoGRAMplusC4D[2]	
rs3798220		LPA	C	T	0.01	1.51	CARDIoGRAM[1]	Lipids
rs10455872		LPA	C	T	0.07	1.45	IBC 50k CAD	Lipids
rs11556924		ZC3HC1	C	T	0.63	1.09	CARDIoGRAMplusC4D[2]	Lipids, Blood Pressure
rs4977574		CDKN2A	G	A	0.45	1.29	CARDIoGRAM[1]	
rs579459		ABO	C	T	0.23	1.07	CARDIoGRAMplusC4D[2]	Lipids, Blood Pressure
rs501120	rs1746048 (1)	CXCL12	C	T	0.86	1.07	CARDIoGRAMplusC4D[2]	
rs12413409		CYP17A1	G	A	0.89	1.12	CARDIoGRAM[1]	Blood Pressure
rs964184		APOA5	G	C	0.13	1.13	CARDIoGRAM[1]	Lipids
rs2259816		HNF1A	T	G	0.35	1.08	Erdmann et al. (2009)	Lipids
rs3184504		SH2B3	T	C	0.48	1.07	CARDIoGRAMplusC4D[2]	Lipids, Blood Pressure
rs4773144		COL4A1	G	A	0.41	1.07	CARDIoGRAMplusC4D[2]	
rs2895811		HHIPL1	C	T	0.45	1.06	CARDIoGRAMplusC4D[2]	
rs3825807		ADAMTS7	A	G	0.57	1.08	CARDIoGRAM[1]	Type 2 Diabetes
rs12936587		RASD1	G	A	0.53	1.06	CARDIoGRAMplusC4D[2]	
rs216172		SMG6	C	G	0.36	1.07	CARDIoGRAM[1]	
rs46522	rs318090 (1)	UBE2Z	A	G	0.52	1.06	CARDIoGRAM[1]	
rs1122608		LDLR	G	T	0.77	1.1	CARDIoGRAMplusC4D[2]	Lipids, Type 2 Diabetes
rs9982601		KCNE2	T	C	0.14	1.13	CARDIoGRAMplusC4D[2]	
rs4845625		IL6R	T	C	0.43	1.04	CARDIoGRAMplusC4D[2]	
rs1561198	rs2028900 (0.95)	GGCX/VAMP8	T	C	0.43	1.05	CARDIoGRAMplusC4D[2]	
rs6544713	rs4299376 (1)	ABCG8	G	T	0.29	1.06	CARDIoGRAMplusC4D[2]	Lipids

Lead SNP	Proxy SNP (r^2)	Gene	Risk Allele	Other Allele	Risk Allele Frequency	Risk Estimate (published)	Reference	Pleiotropy*
rs515135		APOB	C	T	0.83	1.08	CARDIoGRAMplusC4D[2]	Lipids
rs2252641		ZEB2-AC074093.1	C	T	0.44	1.04	CARDIoGRAMplusC4D[2]	
rs1878406		EDNRA	T	C	0.13	1.06	CARDIoGRAMplusC4D[2]	
rs7692387		GUCY1A3	G	A	0.8	1.06	CARDIoGRAMplusC4D[2]	Blood Pressure
rs273909		SLC22A4/SLC22A5	G	A	0.13	1.09	CARDIoGRAMplusC4D[2]	Lipids
rs10947789		KCNK5	T	C	0.75	1.06	CARDIoGRAMplusC4D[2]	
rs2048327		SLC22A3/LPAL2/LPA	C	T	0.41	1.06	CARDIoGRAMplusC4D[2]	Lipids
rs4252120		PLG	T	C	0.71	1.06	CARDIoGRAMplusC4D[2]	
rs2023938	rs11984041 (0.86)	HDAC9	T	C	0.09	1.07	CARDIoGRAMplusC4D[2]	
rs10953541		BCAP29	C	T	0.75	1.08	CAD C4D[5]	Lipids
rs2954029		TRIB1	A	T	0.52	1.04	CARDIoGRAMplusC4D[2]	Lipids, Blood Pressure
rs3217992		CDKN2BAS	T	C	0.34	1.16	CARDIoGRAMplusC4D[2]	Type 2 Diabetes
rs2505083	rs2487928 (0.88)	KIAA1462	A	G	0.44	1.06	CARDIoGRAMplusC4D[2]	
rs2047009		CXCL12	G	T	0.51	1.05	CARDIoGRAMplusC4D[2]	
rs2246833	rs1412444 (0.98)	LIPA	T	C	0.35	1.06	CARDIoGRAMplusC4D[2]	
rs974819	rs11226029 (1)	PDGFD	G	A	0.26	1.07	CARDIoGRAMplusC4D[2]	
rs9319428		FLT1	A	G	0.32	1.05	CARDIoGRAMplusC4D[2]	
rs9515203		COL4A1/COL4A2	T	C	0.71	1.08	CARDIoGRAMplusC4D[2]	
rs7173743		ADAMTS7	T	C	0.58	1.07	CARDIoGRAMplusC4D[2]	
rs17514846		FURIN/FES	A	C	0.46	1.05	CARDIoGRAMplusC4D[2]	Blood Pressure

*Obtained from phenoscanner (http://www.phenoscanner.medschl.cam.ac.uk/ accessed September 1, 2017) using $p < 0.001$ as cutoff.

References:

1: Schunkert H, König IR, Kathiresan S, Reilly MP, Assimes TL, Holm H, et al. Large-scale association analysis identifies 13 new susceptibility loci for coronary artery disease. *Nat Genet*. 2011; 43:333-338

2: CARDIoGRAMplusC4D Consortium, Deloukas P, Kanoni S, Willenborg C, Farrall M, Assimes TL, Thompson JR, et al. Large-scale association analysis identifies new risk loci for coronary artery disease. *Nat Genet*. 2013; 45:25-33

3: The IBC 50K CAD Consortium. Large-scale gene-centric analysis identifies novel variants for coronary artery disease. *PLOS Genet*. 2011;7(9): e1002260

4: Erdmann J, Grosshennig A, Braund PS, König IR, Hengstenberg C, Hall AS, et al. New susceptibility locus for coronary artery disease on chromosome 3q22.3. *Nat Genet*. 2009; 41:280-2

5: Coronary Artery Disease (C4D) Genetics Consortium. A genome-wide association study in Europeans and South Asians identifies five new loci for coronary artery disease. *Nat Genet*. 2011; 43:339-344

Supplemental Table 2. Baseline Characteristics of the Malmö Diet and Cancer Study Male Participants According to Tertiles of the Polygenic Risk Score for Coronary Heart Disease

	PRS-T1	PRS-T2	PRS-T3	Total
n	3110	3111	3110	9331
Age, y (mean ± SD)	59.5 ± 7.2	59.1 ± 7.0	58.8 ± 7.0	59.1 ± 7.1
BMI, kg/m^2 (mean ± SD)	26.2 ± 3.5	26.3 ± 3.5	26.2 ± 3.5	26.2 ± 3.5
SBP, mmHg (mean ± SD)	144 ± 20	144 ± 19	144 ± 19	144 ± 20
DBP, mmHg (mean ± SD)	88 ± 10	88 ± 10	88 ± 10	88 ± 10
ApoA-I, µmol/L (mean ± SD)	51.8 ± 8.6	51.8 ± 8.9	52.1 ± 9.3	51.8 ± 8.9
ApoB, µmol/L (mean ± SD)	2.12 ± 0.49	2.14 ± 0.49	2.18 ± 0.49	2.16 ± 0.49
Triglycerides, mmol/L (mean ± SD)	1.5 ± 0.8	1.6 ± 0.9	1.6 ± 1.0	1.53 ± 0.93
AHT, n (%)	552 (17.8)	565 (18.2)	567 (18.2)	1684 (18.1)
Lipid lowering medication, n (%)	76 (2.4)	113 (3.6)	93 (3.0)	282 (3.0)
Prevalent diabetes, n (%)	170 (5.5)	185 (6.0)	161 (5.2)	516 (5.5)
Incident CHD, n (%)	523 (16.8)	647 (20.8)	795 (25.6)	1965 (21.1)
Smoking				
Never, n (%)	924 (29.7)	865 (27.8)	906 (29.1)	2695 (28.9)
Former, n (%)	1303 (41.9)	1307 (42.0)	1340 (43.1)	3950 (42.3)
Current, n (%)	883 (28.4)	939 (30.2)	864 (27.8)	2686 (28.8)

PRS, polygenic risk score; T, tertile; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ApoA-I, apolipoprotein A-I; ApoB, apolipoprotein B; AHT, antihypertensive medication; CHD, coronary heart disease

Supplemental Table 3. Baseline Characteristics of the Malmö Diet and Cancer Study Female Participants According to Tertiles of the Polygenic Risk Score for Coronary Heart Disease

	PRS-T1	PRS-T2	PRS-T3	Total
n	5037	5038	5037	15112
Age, y (mean ± SD)	57.4 ± 8.0	57.3 ± 8.0	57.2 ± 8.0	57.3 ± 8.0
BMI, kg/m^2 (mean ± SD)	25.4 ± 4.3	25.4 ± 4.3	25.5 ± 4.3	25.5 ± 4.3
SBP, mmHg (mean ± SD)	139 ± 20	139 ± 21	139 ± 20	139 ± 20
DBP, mmHg (mean ± SD)	84 ± 10	84 ± 10	84 ± 10	84 ± 10
ApoA-I, µmol/L (mean ± SD)	58.9 ± 10	58.9 ± 9.6	58.6 ± 9.6	58.7 ± 10
ApoB, µmol/L (mean ± SD)	2.01 ± 0.51	2.05 ± 0.51	2.07 ± 0.51	2.05 ± 0.51
Triglycerides, mmol/L (mean ± SD)	1.25 ± 0.64	1.23 ± 0.74	1.29 ± 0.72	1.26 ± 0.70
AHT, n (%)	825 (16.4)	771 (15.3)	801 (15.9)	2397 (15.9)
Lipid lowering medication, n (%)	72 (1.4)	80 (1.6)	107 (2.1)	259 (1.7)
Prevalent diabetes, n (%)	167 (3.3)	159 (3.2)	168 (3.3)	494 (3.3)
Incident CHD, n (%)	346 (6.9)	392 (7.8)	514 (10.2)	1252 (8.3)
Smoking				
Never, n (%)	2215 (44.0)	2265 (45.0)	2252 (44.7)	6732 (44.6)
Former, n (%)	1375 (27.3)	1386 (27.5)	1428 (28.4)	4189 (27.7)
Current, n (%)	1447 (28.7)	1387 (27.5)	1357 (26.9)	4191 (27.7)

PRS, polygenic risk score; T, tertile; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ApoA-I, apolipoprotein A-I; ApoB, apolipoprotein B; AHT, antihypertensive medication; CHD, coronary heart disease

Supplemental Table 4. Baseline Characteristics of the Malmö Diet and Cancer Study Male Participants According to Smoking Status

	Never	Former	Current	Total
n	2695	3950	2686	9331
Age, y (mean ± SD)	59.2 ± 7.0	59.9 ± 7.3	58.0 ± 6.7	59.1 ± 7.1
BMI, kg/m^2 (mean ± SD)	26.1 ± 3.4	26.8 ± 3.4	25.5 ± 3.5	26.2 ± 3.5
SBP, mmHg (mean ± SD)	143 ± 19	146 ± 20	142 ± 20	144 ± 20
DBP, mmHg (mean ± SD)	88 ± 10	88 ± 10	87 ± 10	88 ± 10
ApoA-I, µmol/L (mean ± SD)	51.8 ± 8.6	52.5 ± 8.6	51.1 ± 9.3	51.8 ± 8.9
ApoB, µmol/L (mean ± SD)	2.09 ± 0.47	2.16 ± 0.51	2.20 ± 0.51	2.16 ± 0.49
Triglycerides, mmol/L (mean ± SD)	1.41 ± 0.71	1.56 ± 0.90	1.61 ± 1.14	1.53 ± 0.93
AHT, n (%)	491 (18.2)	794 (20.1)	399 (14.9)	1684 (18.1)
Lipid lowering medication, n (%)	67 (2.5)	132 (3.3)	83 (3.1)	282 (3.0)
Prevalent diabetes, n (%)	135 (5.0)	254 (6.4)	127 (4.7)	516 (5.5)
Incident CHD, n (%)	475 (17.6)	821 (20.8)	669 (24.9)	1965 (21.1)
Tertile of PRS				
T1, n (%)	924 (34.3)	1303 (33.0)	883 (32.9)	3110 (33.3)
T2, n (%)	865 (32.1)	1307 (33.1)	939 (35.0)	3111 (33.3)
T3, n (%)	906 (33.6)	1340 (33.9)	864 (32.1)	3110 (33.3)

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ApoA-I, apolipoprotein A-I; ApoB, apolipoprotein B; AHT, antihypertensive medication; CHD, coronary heart disease; PRS, polygenic risk score; T, tertile

Supplemental Table 5. Baseline Characteristics of the Malmö Diet and Cancer Study Female Participants According to Smoking Status

	Never	Former	Current	Total
n	6732	4189	4191	15112
Age, y (mean ± SD)	58.9 ± 8.1	56.7 ± 8.0	55.4 ± 7.4	57.3 ± 8.0
BMI, kg/m^2 (mean ± SD)	25.8 ± 4.3	25.7 ± 4.2	24.7 ± 4.2	25.5 ± 4.3
SBP, mmHg (mean ± SD)	142 ± 20	138 ± 20	136 ± 20	139 ± 20
DBP, mmHg (mean ± SD)	85 ± 10	84 ± 10	83 ± 10	84 ± 10
ApoA-I, µmol/L (mean ± SD)	58.9 ± 9.6	59.6 ± 10	57.1 ± 10	58.7 ± 10
ApoB, µmol/L (mean ± SD)	2.05 ± 0.51	1.97 ± 0.51	2.09 ± 0.51	2.05 ± 0.51
Triglycerides, mmol/L (mean ± SD)	1.25 ± 0.70	1.22 ± 0.65	1.31 ± 0.75	1.26 ± 0.70
AHT, n (%)	1209 (18.0)	673 (16.1)	515 (12.3)	2397 (15.9)
Lipid lowering medication, n (%)	107 (1.6)	89 (2.1)	63 (1.5)	259 (1.7)
Prevalent diabetes, n (%)	233 (3.5)	144 (3.4)	117 (2.8)	494 (3.3)
Incident CHD, n (%)	506 (7.5)	327 (7.8)	419 (10.0)	1252 (8.3)
Tertile of PRS				
T1, n (%)	2215 (32.9)	1375 (32.8)	1447 (34.5)	5037 (33.3)
T2, n (%)	2265 (33.7)	1386 (33.1)	1387 (33.1)	5038 (33.3)
T3, n (%)	2252 (33.5)	1428 (34.1)	1357 (32.4)	5037 (33.3)

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ApoA-I, apolipoprotein A-I; ApoB, apolipoprotein B; AHT, antihypertensive medication; CHD, coronary heart disease; PRS, polygenic risk score; T, tertile

Supplemental Table 6. Association between Smoking Status and Coronary Heart Disease in Tertiles of Polygenic Risk Score among Men

PRS	Smoking	OR (95% CI) †	*P*Value
T1 *			
	Never	1.00 (ref)	
	Former	1.59 (1.23–2.04)	3×10^{-4}
	Current	2.17 (1.66–2,84)	1.2×10^{-8}
	Per category	1.46 (1.28–1.67)	1.1×10^{-8}
T2			
	Never	1.00 (ref)	
	Former	1.11 (0.89–1.40)	0.35
	Current	1.70 (1.34–2.16)	1×10^{-5}
	Per category	1.32 (1.17–1.49)	7.0×10^{-6}
T3			
	Never	1.00 (ref)	
	Former	1.03 (0.84–1.25)	0.80
	Current	1.31 (1.05–1.62)	0.017
	Per category	1.14 (1.02–1.28)	0.017

* T1, T2, T3 designate the first, second and third tertiles of the polygenic risk score

† Odds ratio and 95% confidence interval for coronary heart disease among former or current smokers compared to never smokers

Model adjusted for age, sex, total energy intake, alcohol intake, leisure-time physical activity, and education

Supplemental Table 7. Association between Smoking Status and Coronary Heart Disease in Tertiles of Polygenic Risk Score among Women

PRS	Smoking	OR (95% CI) †	*P*Value
T1 *			
	Never	1.00 (ref)	
	Former	1.27 (0.95–1.69)	0.11
	Current	1.95 (1.49–2.55)	9.7×10^{-7}
	Per category	1.39 (1.22–1.60)	1.0×10^{-6}
T2			
	Never	1.00 (ref)	
	Former	1.02 (0.77–1.35)	0.90
	Current	2.06 (1.60–2.64)	1.8×10^{-8}
	Per category	1.42 (1.25–1.62)	9.3×10^{-8}
T3			
	Never	1.00 (ref)	
	Former	1.45 (1.15–1.83)	0.001
	Current	1.63 (1.29–2.06)	4×10^{-5}
	Per category	1.29 (1.15–1.44)	2×10^{-5}

* T1, T2, T3 designate the first, second and third tertiles of the polygenic risk score

† Odds ratio and 95% confidence interval for coronary heart disease among former or current smokers compared to never smokers

Model adjusted for age, sex, total energy intake, alcohol intake, leisure-time physical activity, and education

Supplemental Table 8. Association between Smoking Status and Coronary Heart Disease in Tertiles of Polygenic Risk Score among Individuals with no Family History for Myocardial Infarction

PRS	Smoking	OR (95% CI) †	*P*Value
T1 *			
	Never	1.00 (ref)	
	Former	1.51 (1.17–1.95)	0.001
	Current	2.17 (1.68–2.79)	2.4×10^{-9}
	Per category	1.47 (1.30–1.68)	2.1×10^{-9}
T2			
	Never	1.00 (ref)	
	Former	1.05 (0.84–1.33)	0.62
	Current	1.71 (1.36–2.15)	3.6×10^{-6}
	Per category	1.32 (1.17–1.48)	3.3×10^{-6}
T3			
	Never	1.00 (ref)	
	Former	1.11 (0.90–1.35)	0.33
	Current	1.46 (1.18–1.80)	4×10^{-4}
	Per category	1.21 (1.09–1.34)	5×10^{-4}

* T1, T2, T3 designate the first, second and third tertiles of the polygenic risk score

† Odds ratio and 95% confidence interval for coronary heart disease among former or current smokers compared to never smokers

Model adjusted for age, sex, total energy intake, alcohol intake, leisure-time physical activity, and education

Supplemental Table 9. Association between Smoking Status and Coronary Heart Disease in Tertiles of Polygenic Risk Score among Individuals with Family History for Myocardial Infarction

PRS	Smoking	OR (95% CI) †	*P*Value
T1 *			
	Never	1.00 (ref)	
	Former	1.20 (0.91–1.58)	0.20
	Current	1.99 (1.51–2.63)	1.4×10^{-6}
	Per category	1.41 (1.23–1.63)	1.8×10^{-6}
T2			
	Never	1.00 (ref)	
	Former	1.19 (0.91–1.54)	0.20
	Current	1.82 (1.40–2.38)	9.2×10^{-6}
	Per category	1.35 (1.18–1.4)	1.2×10^{-5}
T3			
	Never	1.00 (ref)	
	Former	1.14 (0.91–1.43)	0.26
	Current	1.41 (1.11–1.81)	0.006
	Per category	1.19 (1.05–1.34)	0.006

* T1, T2, T3 designate the first, second and third tertiles of the polygenic risk score

† Odds ratio and 95% confidence interval for coronary heart disease among former or current smokers compared to never smokers

Model adjusted for age, sex, total energy intake, alcohol intake, leisure-time physical activity, and education

Supplemental Table 10. C-statistics and Discrimination by Polygenic Risk Score for Incident Coronary Heart Disease by Smoking Status among Men

	AUC (95%CI)		IDI (SE)	*P*Value
	Traditional Model *	Traditional Model + PRS		
Never Smokers	0.675 (0.649-0.700)	0.702 (0.676-0.727)	0.023 (0.004)	3×10^{-11}
Former Smokers	0.664 (0.644-0.685)	0.673 (0.652-0.693)	0.007 (0.001)	4×10^{-06}
Current Smokers	0.661 (0.637-0.685)	0.664 (0.640-0.688)	0.004 (0.001)	0.003

* Traditional model includes: age, sex, family history of myocardial infarction, systolic blood pressure, antihypertensive medication, ApoB as a proxy for LDL cholesterol, ApoA-I as a proxy for HDL cholesterol and diabetes at baseline

AUC, area under receiver operating curve; CI, confidence interval; IDI: integrated discrimination improvement; PRS, polygenic risk score

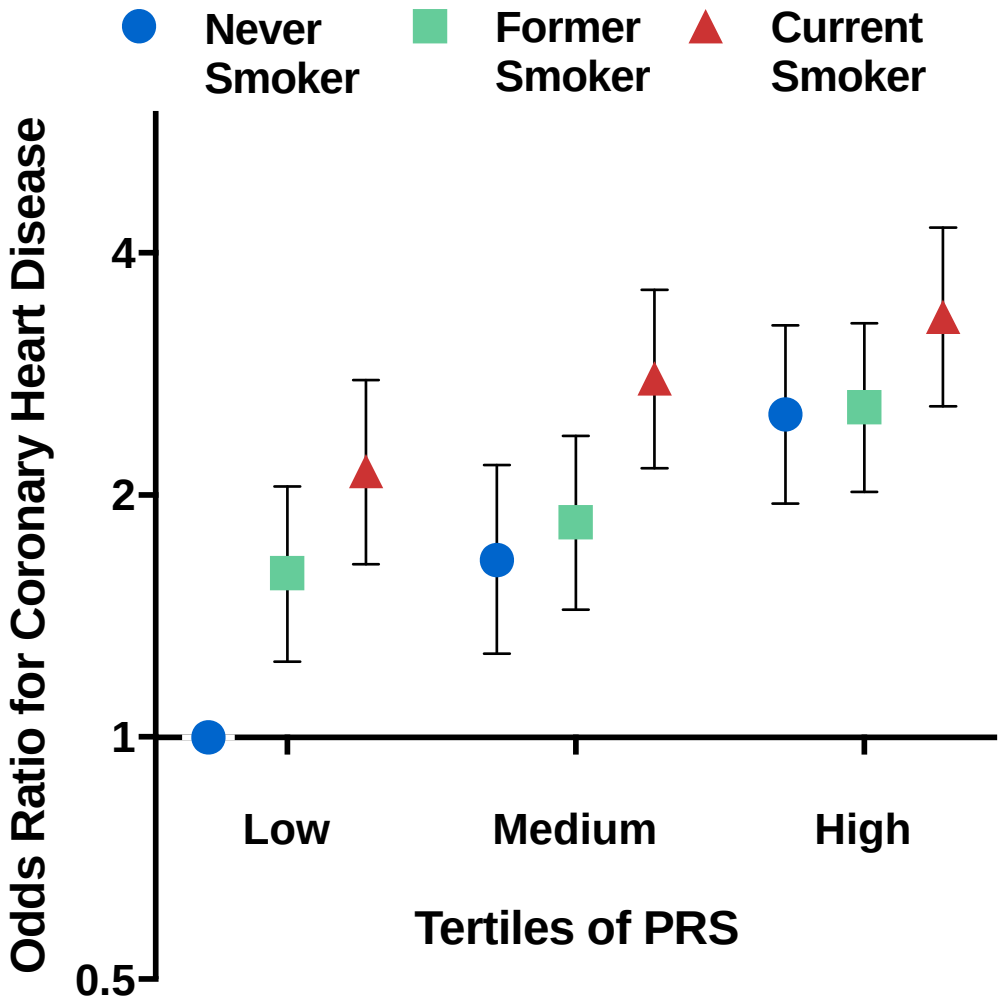
Supplemental Table 11. C-statistics and Discrimination by Polygenic Risk Score for Incident Coronary Heart Disease by Smoking Status among Women

	AUC (95%CI)		IDI (SE)	*P*Value
	Traditional Model *	Traditional Model + PRS		
Never Smokers	0.745 (0.725-0.765)	0.753 (0.732-0.773)	0.005 (0.001)	0.0001
Former Smokers	0.755 (0.727-0.782)	0.764 (0.737-0.790)	0.006 (0.002)	0.004
Current Smokers	0.729 (0.704-0.754)	0.734 (0.710-0.759)	0.004 (0.001)	0.003

* Traditional model includes: age, sex, family history of myocardial infarction, systolic blood pressure, antihypertensive medication, ApoB as a proxy for LDL cholesterol, ApoA-I as a proxy for HDL cholesterol and diabetes at baseline

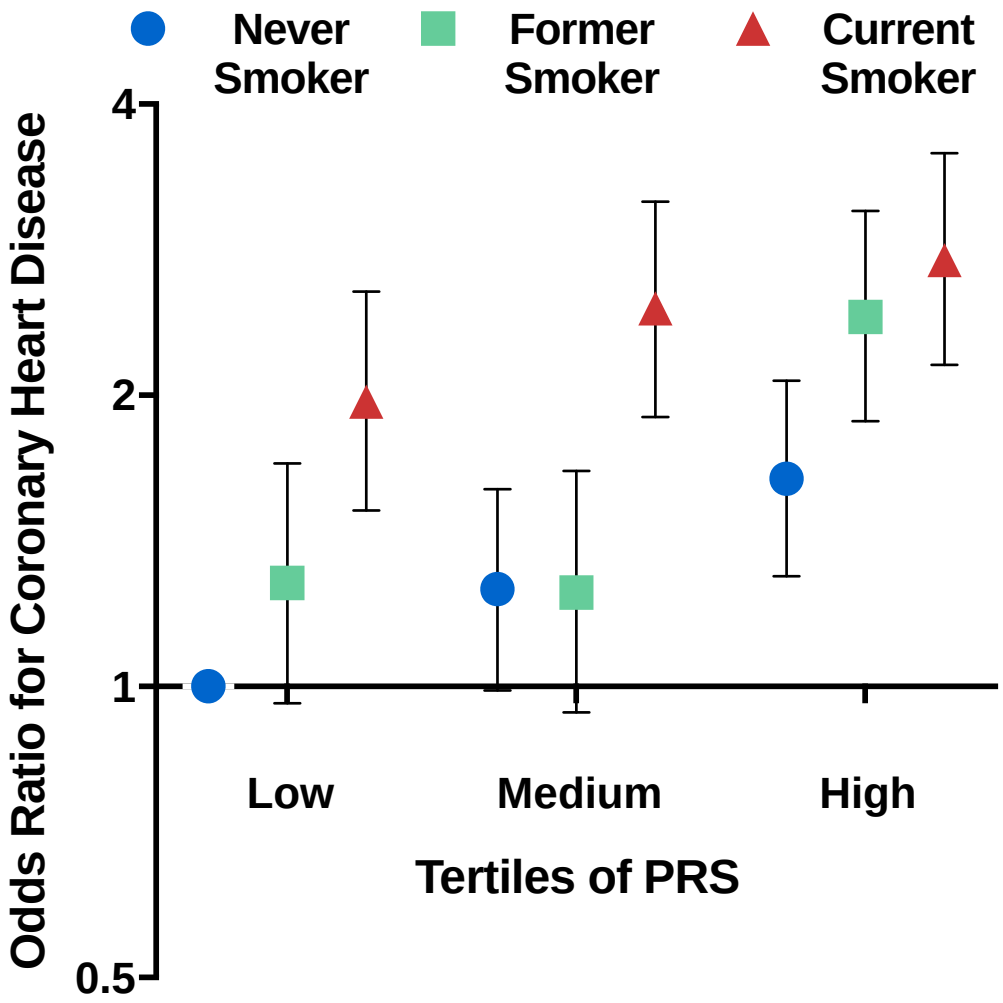
AUC, area under receiver operating curve; CI, confidence interval; IDI: integrated discrimination improvement; PRS, polygenic risk score

Supplemental Figure 1. Odds Ratio for Coronary Heart Disease According to Tertiles of Polygenic Risk Score and Smoking Status among Men



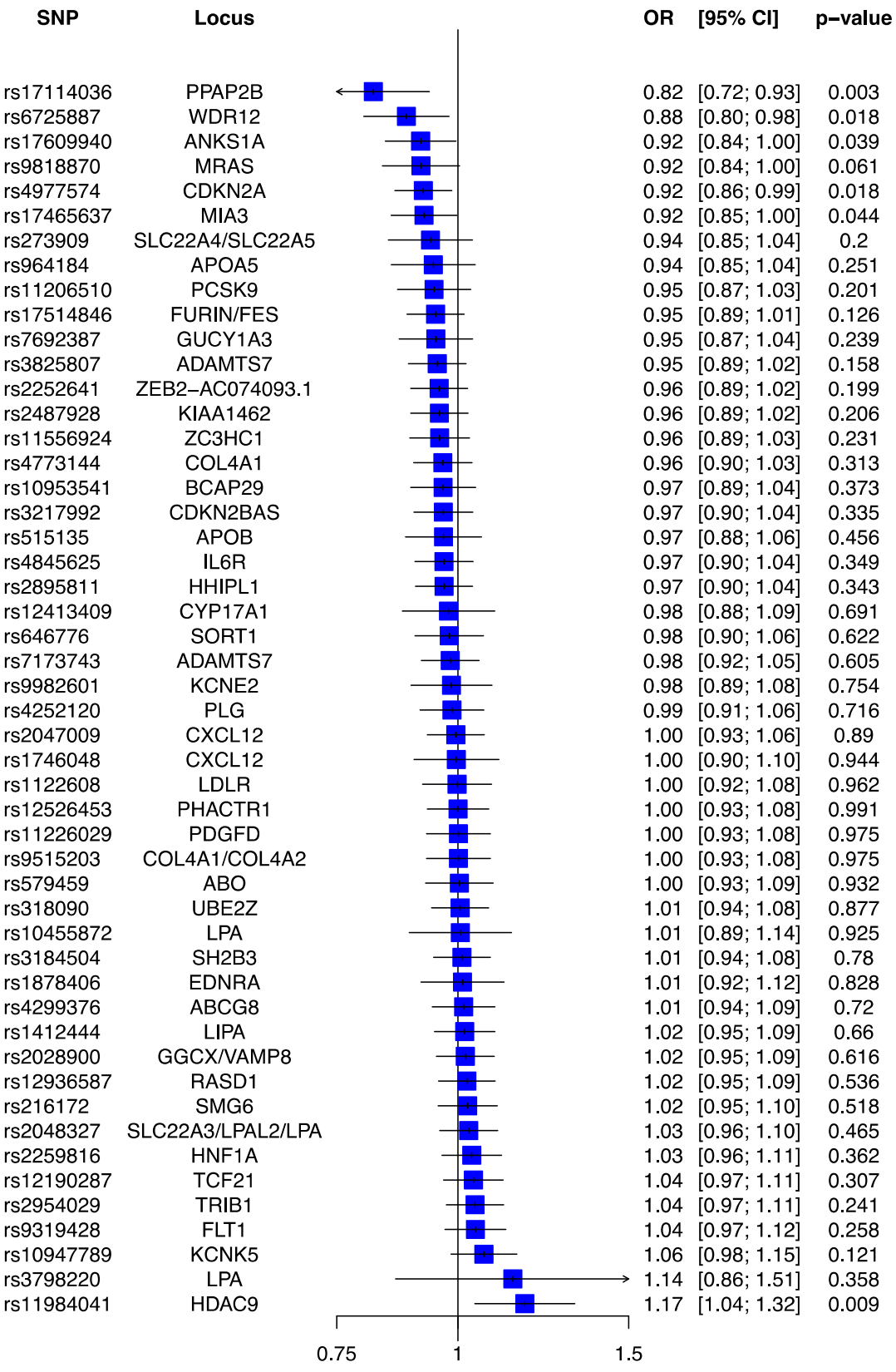
Individuals who are in the lowest tertile of polygenic risk score (PRS) and are never smokers were considered as a reference group. Smoking was associated with higher risk for coronary heart disease among individuals within each tertile of PRS. The magnitude of risk relative risk increase by smoking was higher among men with low PRS (OR: 1.46; 95% CI: 1.28–1.67) compared to men with high PRS (OR: 1.14; 1.02–1.28).

Supplemental Figure 2. Odds Ratio for Coronary Heart Disease According to Tertiles of Polygenic Risk Score and Smoking Status among Women

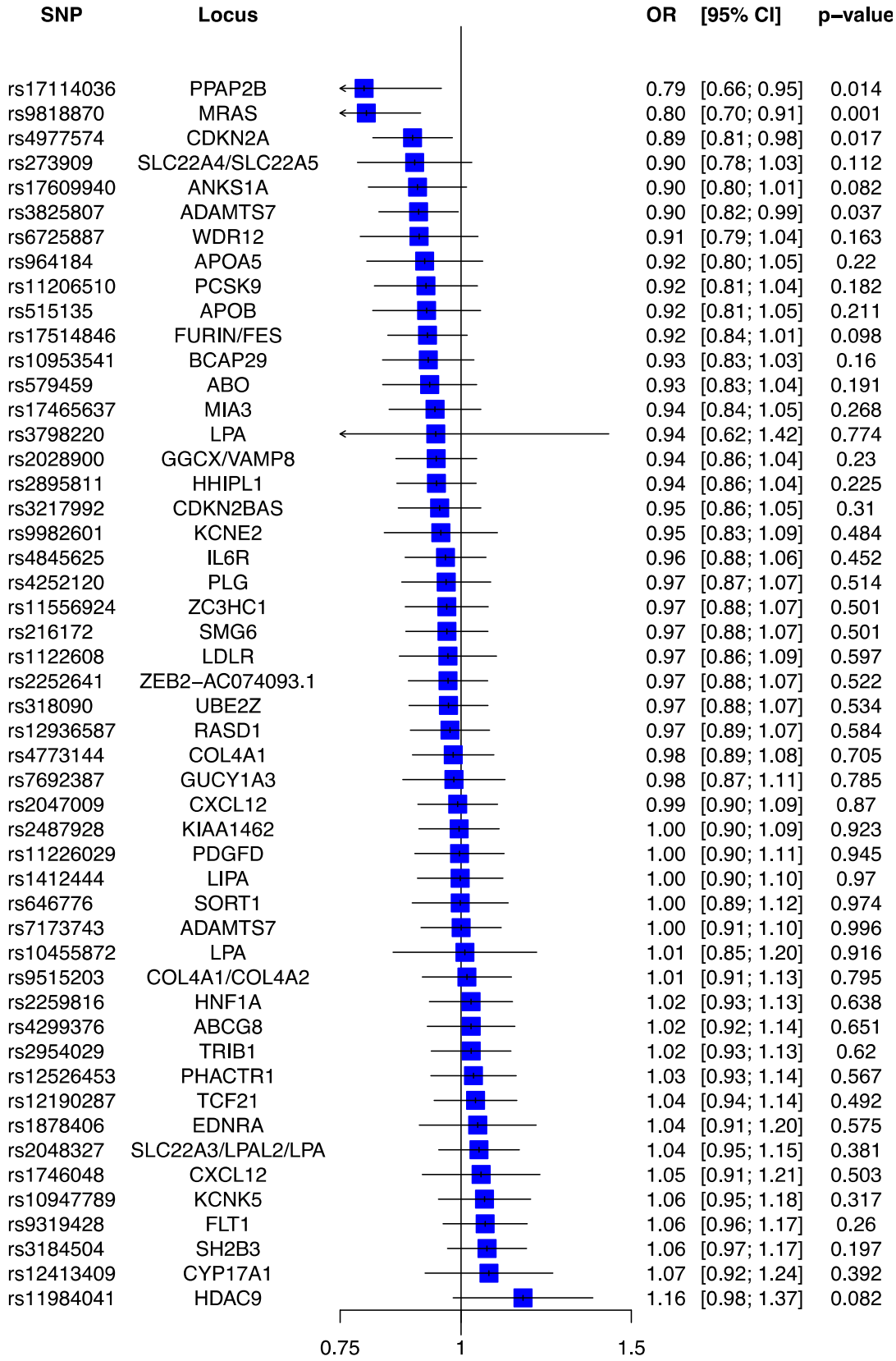


Individuals who are in the lowest tertile of polygenic risk score (PRS) and are never smokers were considered as a reference group. Smoking was associated with higher risk for coronary heart disease among individuals within each tertile of PRS. The magnitude of risk relative risk increase by smoking was higher among women with low PRS (OR: 1.39; 95% CI: 1.22–1.60) compared to women with low PRS (OR: 1.29; 1.15–1.44).

Supplemental Figure 3. Interaction Estimates between each Single Nucleotide Polymorphism and Smoking Status on the Risk of Coronary Heart Disease



Supplemental Figure 4. Interaction Estimates between each Single Nucleotide Polymorphism and Smoking Status on the Risk of Coronary Heart Disease among Men



Supplemental Figure 5. Interaction Estimates between each Single Nucleotide Polymorphism and Smoking Status on the Risk of Coronary Heart Disease among Women