SUPPLEMENTAL MATERIAL

A Twelve-SNP Genetic Risk Score Identifies Individuals at Increased Risk for Future Atrial Fibrillation and Stroke

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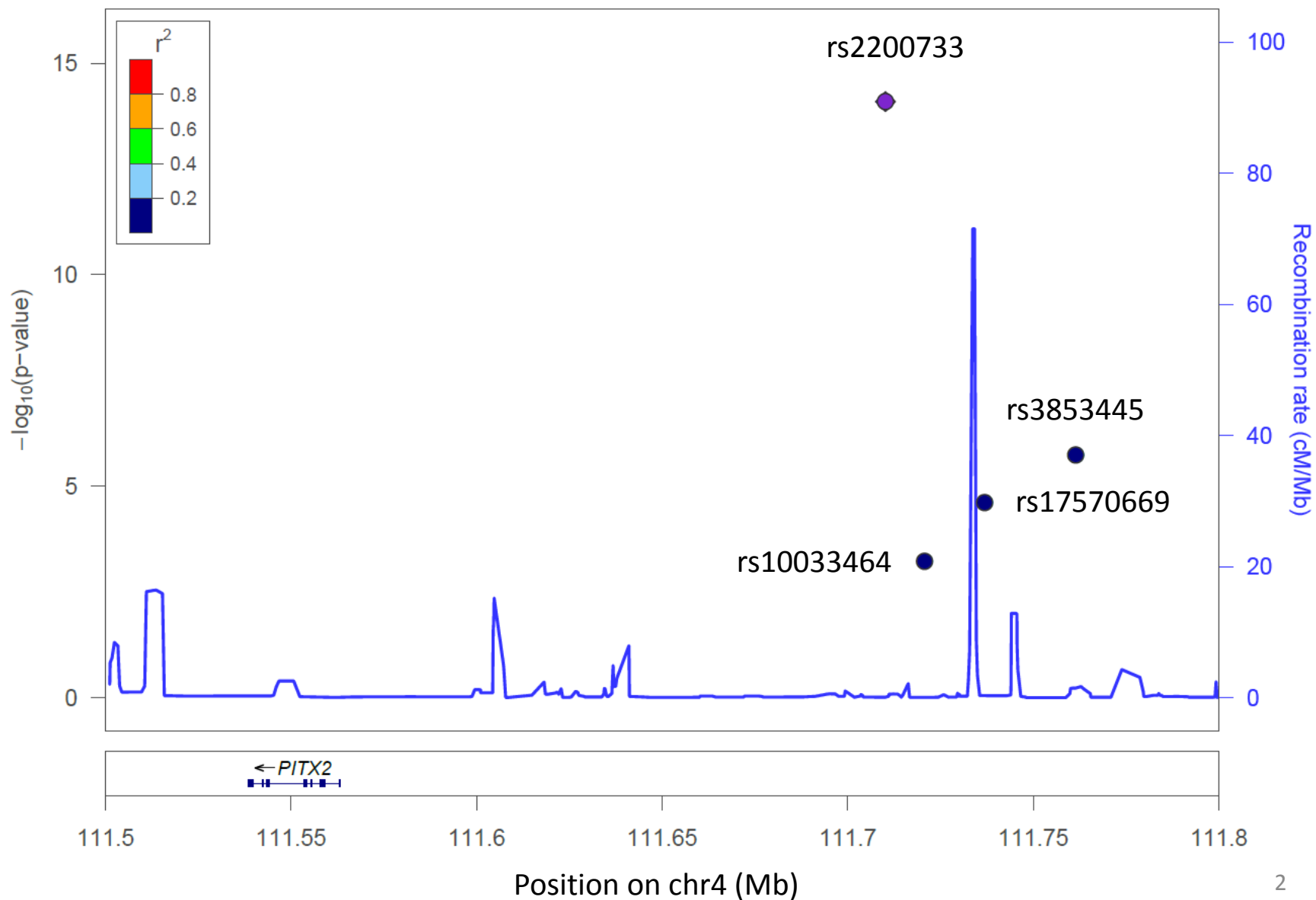[8]Department of Internal Medicine, Skåne University Hospital, Malmö, Sweden;
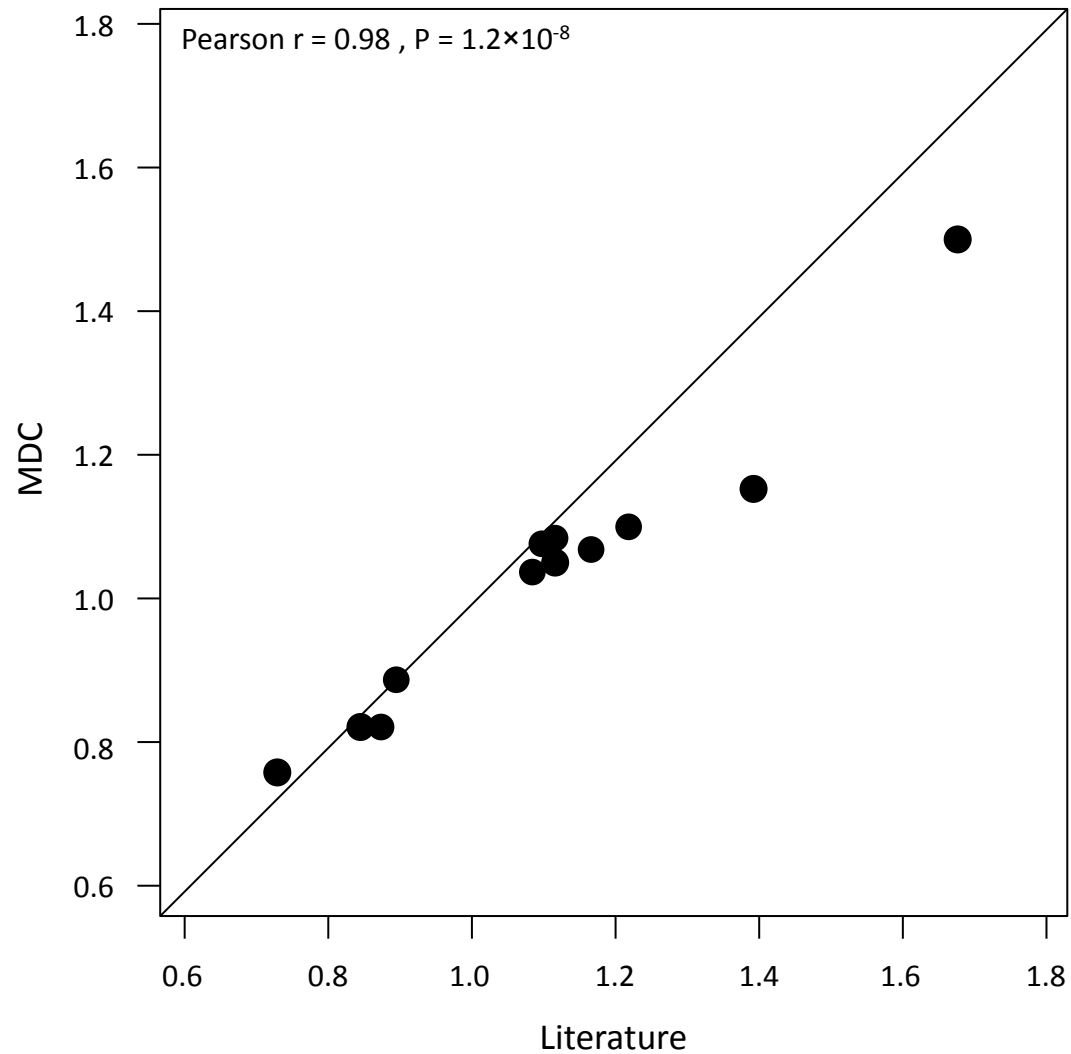*These four authors contributed equally to this manuscript.

Contents

Supplemental Figure Ⅰ. A locus zoom on 4q25

Supplemental Figure Ⅱ. A comparison of risk estimates for the 12 SNPs from the literature versus those observed in the Malmo Diet and Cancer Study

Pearson r = 0.98 , P = 1.2×10^{-8}

x-axis: Risk estimate from the literature, y-axis: Risk estimate from MDC

Supplemental Figure Ⅲ. Cumulative incident atrial fibrillation events according to AF-GRS
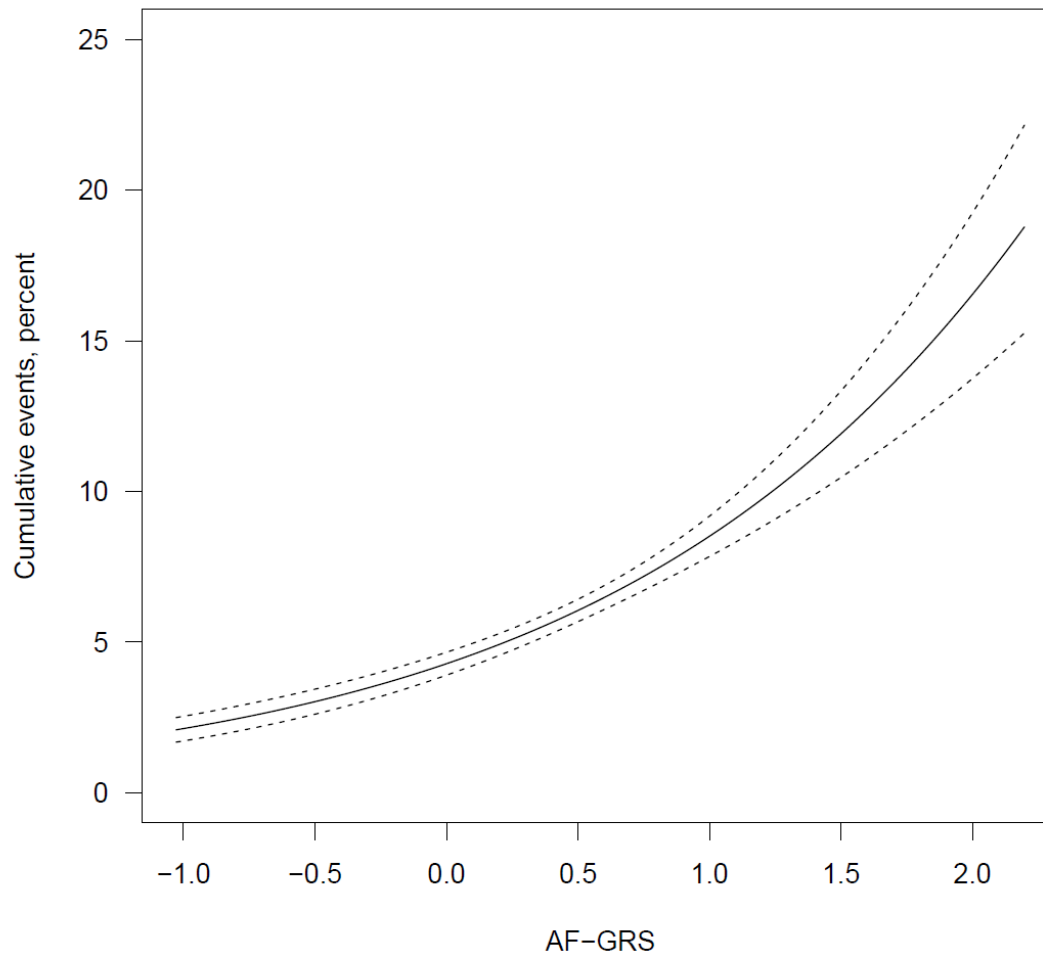
Event rate was adjusted for age, sex, BMI, systolic and diastolic blood pressure, use of antihypertensive medications, current smoking, prevalent diabetes, coronary events, and heart failure. Dotted lines indicate 95% CI the cumulative event rate estimate.

Supplemental Table Ⅰ. Linkage disequilibrium (r^2) between SNPs in the 4q25 locus

SNP	rs10033464	rs17570669	rs3853445
rs2200733	0.01	0.09	0.002
rs10033464		0.01	0.01
rs17570669			0.03

Supplemental Table Ⅱ. Prevalence and contributed weight of each SNP to the AF-GRS in each GRS-quintile

SNP	Modeled allele	Quintile									
		1		2		3		4		5	
		Freq.	Weight	Freq.	Weight	Freq.	Weight	Freq.	Weight	Freq.	Weight
rs13376333	T	0.231	0.0283	0.290	0.0354	0.343	0.0420	0.383	0.0468	0.436	0.0533
rs3903239	G	0.329	0.0431	0.421	0.0551	0.480	0.0629	0.533	0.0699	0.577	0.0756
rs10033464	T	0.020	0.0065	0.049	0.0161	0.074	0.0243	0.142	0.0468	0.186	0.0614
rs2200733	T	0.014	0.0075	0.031	0.0167	0.051	0.0278	0.110	0.0597	0.298	0.1616
rs17570669	T	0.161	-0.0506	0.067	-0.0212	0.054	-0.0169	0.060	-0.0189	0.048	-0.0151
rs3853445	C	0.433	-0.0653	0.301	-0.0454	0.226	-0.0340	0.212	-0.0319	0.152	-0.0230
rs3807989	A	0.516	-0.0543	0.454	-0.0478	0.395	-0.0416	0.352	-0.0371	0.319	-0.0337
rs10821415	A	0.306	0.0319	0.368	0.0384	0.419	0.0437	0.459	0.0479	0.489	0.0510
rs10824026	G	0.250	-0.0348	0.180	-0.0250	0.137	-0.0190	0.124	-0.0172	0.109	-0.0152
rs1152591	A	0.358	0.0437	0.443	0.0542	0.523	0.0640	0.543	0.0663	0.597	0.0730
rs7164883	G	0.077	0.0133	0.133	0.0231	0.173	0.0301	0.216	0.0377	0.267	0.0464
rs2106261	T	0.067	0.0145	0.123	0.0265	0.160	0.0343	0.223	0.0481	0.302	0.0651

Supplemental Table Ⅲ. Risk estimates for atrial fibrillation risk factors

Risk factor	HR (95% CI)	P value
AF-GRS	1.20 (1.16 - 1.24)	3.8×10^{-28}
Age	1.11 (1.10 - 1.12)	1.8×10^{-183}
Male sex	1.70 (1.54 -1.85)	1.1×10^{-29}
BMI	1.06 (1.05 - 1.07)	7.2×10^{-24}
Hypertension	1.43 (1.28 - 1.60)	8.7×10^{-10}
Smoking	1.26 (1.13 - 1.40)	2.7×10^{-05}
Diabetes	1.32 (1.11 - 1.58)	1.6×10^{-03}
CHD	1.69 (1.37 - 2.09)	1.0×10^{-06}
Heart Failure	2.10 (1.53 - 2.87)	3.5×10^{-06}

Risk for AF-GRS is per quintile, age per year, BMI per unit. All other risks are per risk category.
Risk estimates are from a Cox proportional hazards model that included all the variables listed in the table.
Hypertension was defined as systolic blood pressure ≥140mmHg, diastolic blood pressure ≥90mmHg, or use of antihypertensive medications.

Supplemental Table Ⅳ. Stroke event rates according to median age, AF-GRS group, and hypertension

Hypertension	AF-GRS Group*	Ischemic Stroke Event Rate (95%CI)		Likely Cardioembolic Stroke† Event Rate (95%CI)	
		Age < 57.5 years	Age ≥ 57.5 years	Age < 57.5 years	Age ≥ 57.5 years
Yes	Top	2.91 (2.18 - 3.81)	9.01 (7.84 - 10.31)	0.49 (0.24 – 0.87)	2.11 (1.62-2.69)
Yes	Bottom	2.48 (1.79 - 3.34)	7.62 (6.59 - 8.76)	0.19 (0.05 – 0.47)	1.04 (0.72 – 1.46)
No	Top	1.11 (0.7 - 1.68)	4.06 (2.85 - 5.59)	0.20 (0.07 – 0.47)	1.22 (0.67 – 2.05)
No	Bottom	0.83 (0.47 - 1.35)	2.73 (1.74 - 4.06)	0.04 (0.00 – 0.23)	0.28 (0.06 – 0.8)

Event rate is per 1,000 person-years.
Hypertension defined as systolic blood pressure ≥140mmHg, diastolic blood pressure ≥90mmHg, or use of antihypertensive medications.
* Top is top quintile for ischemic stroke events and top quartile for likely cardioembolic stroke events
†Ischemic stroke events that were preceded or coincided with a diagnosis of AF

Supplemental Table Ⅴ. Risk of likely cardioembolic stroke in patients with AF

	AF-GRS Quintile					P_{trend}
	1	2	3	4	5	
HR (95%CI)	Reference	1.07 (0.68 - 1.68)	0.95 (0.60 - 1.52)	1.03 (0.65 - 1.63)	1.81 (1.20 – 2.73)	0.009
P value (vs. Q1)		0.8	0.8	0.9	0.005	

Quintile boundaries for patients with AF: 1 GRS≤0.2149; 2 GRS>0.2149 and ≤0.4335; 3 GRS >0.4335 and ≤0.6368; 4 GRS>0.6368 and ≤0.8713; 5 GRS >0.8713.
Hazard ratios from Cox proportional hazards models adjusted for age, sex, BMI, systolic and diastolic blood pressure, use of antihypertensive