SUPPLEMENTAL MATERIAL

Content

1. Supplemental Material

Study design and population

The genotyped population was comprised of participants of the ASPirin in Reducing Events in the Elderly (ASPREE) trial. Study design[1] and trial results[2, 3] have been published previously. ASPREE was a randomized double-blind placebo-controlled clinical trial investigating the effect of daily 100mg aspirin on disability-free survival over a median 4.6-years (interquartile range 2.1 years) of follow-up. The trial recruited 19,114 individuals aged ≥70 years (≥ 65 years for US minorities), who had no prior cardiovascular events, and were free from dementia or physical disability at enrolment. Participants had no previous diagnosis of myocardial infarction; heart failure; angina pectoris; stroke; diagnosis of atrial fibrillation; or systolic blood pressure ≥180mmHg. Genetic analyses included 12,792 participants of European ancestry who provided samples and informed consent (Figure I). The study was approved by local Ethics Committees and registered on Clinicaltrials.gov (NCT01038583).

Endpoint

The primary endpoint for this secondary analysis was incident CHD, defined as a composite of incident myocardial infarction or CHD death. CHD death included deaths coded as related to fatal myocardial infarction, sudden cardiac death, rapid cardiac death, or other coronary death. All events were assessed by blinded Adjudication Committees, as described previously[2].

Risk model, genotyping and polygenic risk score

The conventional risk model included age, sex, smoking status (current versus former/never), systolic blood pressure, non-high-density-lipoprotein (HDL)-cholesterol, HDL-cholesterol, diabetes and serum creatinine. Selection of variables was based on prior risk models.[4] Serum creatinine was included based on prior evidence from studies of CHD risk in older individuals.[5, 6] Aspirin treatment had no effect on CHD risk in the ASPREE population, and was therefore not included in the model (Supplementary results). In addition, we also calculated the recently published SCORE2-OP risk score for prediction of 5-years cardiovascular events and recalibrated it based on regional risk (moderate risk for women and high risk for men).[7]

Genotyping was performed on 14,052 DNA samples from ASPREE participants using the Axiom 2.0 Precision Medicine Diversity Research Array (Thermo Fisher Scientific, CA, USA) following standard protocols. Variant calling used a custom pipeline aligned to human reference genome hg38. Samples from 12,792 participants passed the following filters: unrelated; Non-Finnish European genetic descent; minimum age at randomization 70 years;

and self-reported white racial ancestry. To define genetic descent, we performed principal component analysis (PCA) using the 1000 Genomes reference population and excluded ASPREE samples that did not overlap with the Non-Finnish European 1000 Genomes cluster (Supplementary material, Figure II).[8] Directly genotyped data from ASPREE and The 1000 Genomes Project phase 3 (liftover to hg38) were merged and LD pruned ($r^2 < 0.1$) using plink version 1.9[9], followed by using R package SNPrelate.[10] We calculated the Z score for first 2 PCA and excluded samples with ± 2SD (standard deviation) of Z score compared to their respective five major reference population groups from the 1000 Genomes Project that included: Caucasians (Non-Finish Europeans), South Asians, East Asians, African American and Hispanics (Figure II). Imputation was performed using the haplotype reference consortium, European samples (University of Michigan imputation server).[11] Post-imputation QC removed variants with low imputation quality scores ($r^2<0.3$).

We calculated PRS in ASPREE using the metaGRS for CAD[12] consisting of 1.7 million genetic variants downloaded from the Polygenic Score Catalog.[13] In the ASPREE data, 1,745,180 (99.6%) of metaGRS SNPs were present (6,140 and 17 SNPs were removed due to variant ID and allele code mismatch, respectively). Plink version 1.9 was used to calculate the weighted sum for effect size of the number of risk alleles for each variant.[9]

Statistical analyses

Participants with available PRS were included. For continuous variables, the mean and SD are reported. For binary variables, absolute and relative frequencies are provided. Correlation of continuous variables was assessed by Spearman correlation coefficients visualized in a correlation matrix using the package “corrplot”. A multivariable Cox proportional hazards regression model including only predictors from the conventional model was used to evaluate the risk of incident CHD events within 5 years. Continuous variables were used as linear predictors.

The model was re-evaluated after adding the continuous PRS distribution per one SD change, and then by adding a categorical PRS divided into tertiles, using the lowest tertile as the reference group, compared with the second and third (higher risk) tertiles. In the manuscript the PRS refers to the continuous variables, unless states different. The first PRS tertile ranged from -2.73 to < -1.35, the second PRS tertile ranged from 1-35 to < -0.97 and the third PRS tertile ranged from -0.97 to 0.69. We also evaluated the addition of the continuous PRS to the SCORE2-OP risk model. Sensitivity analyses were performed after adding use of antihypertensive drugs, statins and genetic ethnicity PCAs to the multivariable model

(Supplementary material). Kaplan-Meier estimates for the incidence of CHD events within 5 years were calculated using the "survival" package and stratified by PRS tertiles.

The area under the curve (AUC) was calculated for each predictor, for the conventional model, for SCORE2-OP and after addition of the continuous PRS using time-dependent receiver-operating-characteristics. The analyses were repeated for subgroups according to sex and PRS tertiles (Supplementary material). Reclassification analyses were performed to assess the change in risk after adding the PRS to the conventional model. Time-to-event continuous and categorical net reclassification improvement (NRI) was calculated using the "nricens" package. The risk categories or the categorical NRI were chosen based on the observed risk within the ASPREE cohort and were set to <1.5%, 1.5 to 2.49% and ≥2.5%. Interaction effects between sex and model covariables were examined. All analyses were performed using R version 3.6.1.[14]

2. Supplemental Results

When aspirin treatment was added as covariate to the multivariable model, no significant effect on CHD events was found (HR 0.84, 95%CI 0.64-1.10, p=0.20). In sensitivity analyses, including information on intake of antihypertensive drugs or statins, intake of antihypertensives showed to be a predictor for CHD events (HR 1.73, 95%CI 1.29-2.31), but statin intake did not (HR 0.75, 95%CI 0.53-1.07). However, the PRS remained an independent predictor in the model (Table VII). In sensitivity analyses, including information on the ten PCAs, which were used to determine the genetic ethnicity, none of the PCAs was a significant predictor for CHD events and the PRS remained an independent predictor in the model (Table VIII). We examined interaction effects between sex and model covariables but found no interaction effect between sex and the CHD PRS (HR 0.93, 95%CI 0.69-1.24, p=0.60; Table IX).

3. Supplemental Tables

Table I: Baseline characteristics comparing the genotyped population, used for these analyses to those, which were not used.

	Non-genotyped ASPREE population	Genotyped ASPREE population (used for present analyses)	p-value
N	6,322	12,792	
Age (median (IQR))	74.30 [71.50, 78.30]	73.90 [71.70, 77.30]	0.049
Female (%)	3,755 (59.4)	7,027 (54.9)	<0.001
Current smoker (%)	344 (5.4)	391 (3.1)	<0.001
Systolic Blood Pressure, mmHg (mean (SD))	138.64 (16.96)	139.46 (16.27)	0.001
Diastolic Blood Pressure, mmHg (mean (SD))	77.46 (10.01)	77.17 (9.97)	0.058
Diabetes (%)	859 (13.6)	1,186 (9.3)	<0.001
Body Mass Index, kg/m^2 (mean (SD))	28.34 (5.04)	27.97 (4.55)	<0.001
HDL-c, mmol/L (mean (SD))	1.58 (0.46)	1.59 (0.46)	0.235
Non-HDL-c, mmol/L (mean (SD))	3.61 (0.96)	3.69 (0.93)	<0.001
Fasting Glucose, mg/dL (mean (SD))	99.57 (21.96)	98.29 (17.12)	<0.001
Creatinine, mg/dL (median [IQR])	0.90 [0.80, 1.00]	0.90 [0.80, 1.00]	0.170
Family history of MI (%)	157 (2.7)	340 (2.9)	0.450

Abbreviations: IQR = inter quartile range, SD = standard deviation, HDL-c = high density lipoprotein cholesterol, MI = myocardial infarction.

Table II: Multivariable linear regression analyses evaluating the association of cardiovascular risk factors and the PRS.

	Beta coefficient	**p-value**
Age per year increase	-0.0059004	<0.001
Female gender	0.0516470	<0.001
Current Smoking	0.0044832	0.847
Systolic Blood Pressure per 10mmHg	0.0052389	0.036
Non-HDL-c per 1 mmol/L increase	0.0115099	0.010
HDL-c per 1 mmol/L increase	-0.0200539	0.040
Diabetes	0.0304555	0.034
Family history of MI	0.0546153	0.028

Abbreviations: CI = confidence interval, HDL-c = high density lipoprotein cholesterol, MI = myocardial infarction.

Table III. Comparison of metaGRS performance in the older ASPREE population versus five younger studies

	Population	**HR per SD**	**AUC / c-statistic**
Neumann & Riaz et al, 2021	ASPREE N12,792, age ≥70 years	1.24 for incident CAD	AUC=55.72%
1. Inouye et al *JACC* 2018[4]	UK Biobank N480,000	1.58 for incident CAD	C = 0.623
2. Wünnemann et al *CircGenomPrecMed* 2019[5]	French-Canadians from 3 cohorts totaling 3639 prevalent CAD cases and 7382 controls	1.69	AUC 0.56–0.60 for incident / recurrent CAD
3. Dikilitas et al *Am J Hum Genet*, 2020[6]	eMERGE (mean age 48 years) 45,645 EA, 7,597 AA, 2,493 HE	1.53 (EA), 1.53 (HE), 1.27 (AA) incident CAD	0.77 (base model + PRS)
4. Elliott et al *JAMA* 2020[7]	UK Biobank N= 352 660 (mean age, 55.9 years	1.32	C statistic of 0.61
5. Mosely et al *JAMA* 2020[8]	N4847 Europeans aged 45-79 (ARIC), 2390 Multi-Ethnic (MESA)	1.24, 1.38	C statistic of 0.549, 0.587

Table IV: Estimated net reclassification improvement (NRI, continuous and categorical) for risk of 5-year CHD event.

Continuous NRI	**Estimate**	**95%CI**
NRI	0.25	0.15-0.28
NRI+	0.16	0.08-0.20
NRI-	0.09	0.04-0.10
P(Up|Case)	0.58	0.54-0.60
P(Down|Case)	0.42	0.40-0.46
P(Down|Ctrl)	0.54	0.52-0.55
P(Up|Ctrl)	0.46	0.45-0.48
Categorical NRI		
NRI	0.063	0.001-0.129
NRI+	0.044	-0.007-0.105
NRI-	0.019	0.003-0.032
P(Up|Case)	0.106	0.031-0.154
P(Down|Case)	0.062	0.027-0.096
P(Down|Ctrl)	0.084	0.046-0.116
P(Up|Ctrl)	0.066	0.037-0.090

Table V: Baseline characteristics for males and females

	Male	Female	p-value
Number of participants	5,765	7,027	
Age (median (IQR))	73.7 (71.6, 77.0)	74.0 (71.7, 77.6)	0.001
Age categories (%)			
70-74	3,567 (61.9)	4,131 (58.8)	
75-79	1,426 (24.7)	1,845 (26.3)	
80-84	598 (10.4)	816 (11.6)	
>85	174 (3.0)	235 (3.3)	
Current Smoker (%)	198 (3.4)	193 (2.7)	0.028
Systolic Blood Pressure, mmHg (mean (SD))	141.41 (15.78)	137.86 (16.49)	<0.001
Diastolic Blood Pressure, mmHg (mean (SD))	78.07 (9.58)	76.42 (10.21)	<0.001
Diabetes (%)	646 (11.2)	540 (7.7)	<0.001
Body Mass Index, kg/m^2 (mean (SD))	27.93 (3.77)	28.01 (5.10)	0.333
HDL-c mmol/L (mean (SD))	1.40 (0.38)	1.74 (0.46)	<0.001
Non-HDL-c, mmol/L (mean (SD))	3.63 (0.90)	3.73 (0.96)	<0.001
Fasting Glucose, mg/dL (mean (SD))	100.82 (17.99)	96.22 (16.08)	<0.001
Creatinine, mg/dL (mean (SD))	1.02 (0.21)	0.81 (0.17)	<0.001
Familiy history of MI (%)	126 (2.2)	214 (3.0)	0.003
Polygenic Risk Score (mean (SD))	-1.18 (0.45)	-1.14 (0.45)	<0.001

Abbreviations: IQR = inter quartile range, SD = standard deviation, HDL-c = high density lipoprotein cholesterol, MI = myocardial infarction.

Table VI: Hazard ratios for the conventional model, conventional model + continuous PRS and conventional model + categorical PRS in males

	Conventional Model			Conventional Model + continuous PRS			Conventional Model + categorical PRS		
	HR	**95%CI**	**p-value**	**HR**	**95%CI**	**p-value**	**HR**	**95%CI**	**p-value**
Age	1.05	(1.02-1.09)	0.004	1.06	(1.02-1.10)	0.002	1.06	(1.02-1.10)	0.002
Current Smoking	1.99	(0.97-4.07)	0.06	2.03	(0.99-4.15)	0.05	2.02	(0.99-4.13)	0.05
SBP per 10 mmHg increase	0.98	(0.89-1.09)	0.75	0.98	(0.88-1.09)	0.71	0.98	(0.89-1.09)	0.75
Non-HDL-c	1.58	(1.33-1.87)	<0.001	1.57	(1.32-1.86)	<0.001	1.56	(1.32-1.85)	<0.001
HDL-c	0.52	(0.31-0.88)	0.015	0.52	(0.31-0.88)	0.015	0.52	(0.31-0.87)	0.013
Diabetes	0.97	(0.54-1.74)	0.92	0.95	(0.53-1.71)	0.87	0.95	(0.53-1.70)	0.86
Creatinine	1.73	(0.88-3.38)	0.11	1.71	(0.87-3.36)	0.12	1.72	(0.88-3.37)	0.11
PRS (continuous per SD)				1.27	(1.08-1.50)	0.005			
PRS 1st Tertile							1.00	(Reference)	
PRS 2nd Tertile							1.49	(0.97-2.29)	0.07
PRS 3rd Tertile							1.79	(1.17-2.72)	0.007

Table VII: Hazard ratios for the conventional model, conventional model + continuous PRS and conventional model + categorical PRS in females

	Conventional Model			Conventional Model + continuous PRS			Conventional Model + categorical PRS		
	HR	**95%CI**	**p-value**	**HR**	**95%CI**	**p-value**	**HR**	**95%CI**	**p-value**
Age	1.14	(1.09-1.20)	<0.001	1.15	(1.10-1.20)	<0.001	1.15	(1.10-1.20)	<0.001
Current Smoking	2.26	(0.71-7.24)	0.17	2.20	(0.69-7.04)	0.18	2.24	(0.70-7.17)	0.17
SBP per 10 mmHg increase	1.14	(0.99-1.31)	0.07	1.14	(0.99-1.31)	0.07	1.14	(0.99-1.31)	0.06
Non-HDL-c	1.00	(0.78-1.29)	1.00	1.00	(0.77-1.29)	0.99	1.00	(0.77-1.29)	0.99
HDL-c	0.77	(0.44-1.38)	0.39	0.78	(0.44-1.39)	0.40	0.77	(0.43-1.37)	0.38
Diabetes	0.52	(0.16-1.68)	0.27	0.51	(0.16-1.67)	0.27	0.51	(0.16-1.67)	0.27
Creatinine	1.81	(0.55-5.95)	0.33	1.78	(0.55-5.83)	0.34	1.78	(0.55-5.80)	0.34
PRS (continuous per SD)				1.18	(0.92-1.49)	0.19			
PRS 1st Tertile							1.00	(Reference)	
PRS 2nd Tertile							1.37	(0.75-2.52)	0.31
PRS 3rd Tertile							1.36	(0.74-2.49)	0.32

Table VIII: AUC for each predictor, the conventional model and the PRS added to the conventional model in males and females

	Males		Females	
	AUC	**95%CI**	**AUC**	**95%CI**
Age	53.41%	(47.75-59.08)	67.35%	(60.06-74.65)
Current Smoking	51.24%	(49.26-53.22)	51.37%	(48.35-54.40)
Systolic Blood Pressure	48.15%	(42.96-53.34)	57.32%	(50.71-63.93)
Non-HDL-c	63.85%	(58.81-68.89)	50.79%	(43.58-58.00)
HDL-c	58.30%	(53.55-63.05)	50.71%	(43.35-58.08)
Diabetes	49.86%	(47.24-52.49)	51.02%	(48.42-53.62)
Creatinine	54.99%	(49.66-60.34)	56.01%	(49.72-62.30)
PRS	57.15%	(52.20-62.11)	54.98%	(48.21-61.77)
Conventional Model	66.58%	(61.89-71.29)	70.07%	(63.46-76.69)
PRS added to Conventional Model	68.18%	(63.64-72.73)	71.00%	(64.45-77.55)

Table IX: Baseline characteristics according to PRS tertiles

	First tertile	Second tertile	Third tertile	p-value
Number of participants	4,263	4,264	4,264	
Age (median (IQR))	74.1 (71.8, 77.7)	73.8 (71.7, 77.3)	73.7 (71.6, 76.9)	<0.001
Age categories (%)				
70-74	2,458 (57.7)	2,589 (60.7)	2,651 (62.2)	
75-79	1,141 (26.8)	1,073 (25.2)	1,057 (24.8)	
80-84	522 (12.2)	455 (10.7)	436 (10.2)	
>85	142 (3.3)	147 (3.4)	120 (2.8)	
Female (%)	2,239 (52.5)	2,338 (54.8)	2,450 (57.5)	<0.001
Current Smoker (%)	127 (3.0)	132 (3.1)	132 (3.1)	0.937
Systolic Blood Pressure, mmHg (mean (SD))	139.51 (16.36)	139.18 (15.79)	139.68 (16.65)	0.348
Diastolic Blood Pressure, mmHg (mean (SD))	77.15 (10.00)	77.14 (9.83)	77.21 (10.07)	0.944
Diabetes (%)	381 (8.9)	375 (8.8)	430 (10.1)	0.079
Body Mass Index, kg/m^2 (mean (SD))	27.88 (4.57)	27.96 (4.58)	28.07 (4.51)	0.159
HDL-c, mmol/L (mean (SD))	1.58 (0.46)	1.59 (0.46)	1.58 (0.45)	0.369
Non-HDL-c; mmol/L (mean (SD))	3.66 (0.91)	3.69 (0.95)	3.72 (0.94)	0.019
Fasting Glucose, mg/dL (mean (SD))	98.13 (17.10)	98.12 (17.09)	98.64 (17.19)	0.291
Creatinine, mg/dL (mean (SD))	0.91 (0.22)	0.91 (0.22)	0.90 (0.21)	0.113
Family history of MI (%)	103 (2.4)	107 (2.5)	130 (3.0)	0.146
Polygenic Risk Score (mean (SD))	-1.65 (0.24)	-1.16 (0.11)	-0.67 (0.24)	<0.001

Abbreviations: IQR = inter quartile range, SD = standard deviation, HDL-c = high density lipoprotein cholesterol, MI = myocardial infarction.

Table X: AUC for each predictor, the conventional model and the PRS added to the conventional model in individuals from the lowest and highest PRS tertile

	Lowest PRS Tertile		Highest PRS Tertile	
	AUC	**95%CI**	**AUC**	**95%CI**
Age	65.35%	(56.82-73.88)	50.62%	(43.02-58.22)
Sex	61.58%	(55.28-67.89)	64.76%	(59.38-70.15)
Current Smoking	49.99%	(47.72-52.28)	52.67%	(49.58-55.78)
Systolic Blood Pressure	52.86%	(44.97-60.75)	52.81%	(46.34-59.29)
Non-HDL-c	64.85%	(57.54-72.16)	61.68%	(55.62-67.75)
HDL-c	54.94%	(47.13-62.76)	67.20%	(60.82-73.59)
Diabetes	51.94%	(49.67-54.23)	50.61%	(47.47-53.76)
Creatinine	61.06%	(53.22-68.91)	59.35%	(53.36-65.34)
PRS	50.37%	(42.60-58.15)	51.55%	(44.59-58.53)
Conventional Model	76.62%	(70.49-82.76)	73.21%	(67.39-79.03)
PRS added to Conventional Model	77.15%	(71.07-83.23)	73.38%	(67.63-79.15)

Table XI: Sensitivity analyses including information on intake of antihypertensive drugs and statins for calculation of the multivariable Cox regression model.

	HR	95%CI	p-value
Age	1.09	(1.06-1.12)	<0.001
Female Sex	0.44	(0.31-0.61)	<0.001
Current Smoking	2.05	(1.12-3.77)	0.021
SBP per 10 mmHg increase	1.02	(0.94-1.11)	0.57
Non-HDL-c	1.34	(1.15-1.56)	<0.001
HDL-c	0.67	(0.46-0.99)	0.043
Diabetes	0.79	(0.47-1.34)	0.38
Creatinine	1.58	(0.88-2.83)	0.13
PRS (continuous per SD)	1.23	(1.08-1.41)	0.003
Intake of antihypertensives	1.73	(1.29-2.31)	<0.001
Intake of statin	0.75	(0.53-1.07)	0.11

Table XII: Sensitivity analyses including information on PCAs for calculation of the multivariable Cox regression model.

	HR	95%CI	p-value
Age	1.09	(1.06; 1.12)	<0.001
Female Sex	0.46	(0.33; 0.65)	<0.001
Current Smoking	2.02	(1.10; 3.71)	0.024
SBP per 10 mmHg increase	1.04	(0.96; 1.13)	0.36
Non-HDL-c	1.35	(1.17; 1.56)	<0.001
HDL-c	0.64	(0.44; 0.95)	0.025
Diabetes	0.81	(0.48; 1.36)	0.42
Creatinine	1.88	(1.05; 3.35)	0.033
PRS (continuous per SD)	1.25	(1.09; 1.43)	0.002
PCA1	0.87	(0.50; 1.51)	0.61
PCA2	1.00	(0.66; 1.53)	0.98
PCA3	1.14	(0.93; 1.40)	0.19
PCA4	1.12	(0.92; 1.36)	0.27
PCA5	0.98	(0.93; 1.02)	0.28
PCA6	0.98	(0.96; 1.01)	0.24
PCA7	1.00	(0.97; 1.02)	0.79
PCA8	0.99	(0.93; 1.05)	0.70
PCA9	1.00	(0.99; 1.02)	0.56
PCA10	1.01	(0.99; 1.03)	0.61

Table XIII: Interaction of sex with model covariables.

	HR	95% CI	p-value
Age	1.06	(1.02; 1.10)	0.002
Female Sex	0.00	(0.00; 0.06)	0.002
Current Smoking	2.02	(0.99; 4.14)	0.05
SBP per 10 mmHg increase	0.98	(0.88; 1.09)	0.72
Non-HDL-c	1.57	(1.32; 1.86)	<0.001
HDL-c	0.52	(0.31; 0.88)	0.015
Diabetes	0.95	(0.53; 1.70)	0.86
Creatinine	1.71	(0.87; 3.36)	0.12
PRS (continuous per SD)	1.27	(1.08; 1.50)	0.005
Female Sex * Age	1.08	(1.02; 1.15)	0.007
Female Sex * Current Smoking	1.09	(0.28; 4.27)	0.90
Female Sex * SBP per 10 mmHg increase	1.16	(0.98; 1.38)	0.09
Female Sex * Non-HDL-c	0.64	(0.47; 0.86)	0.004
Female Sex * HDL-c	1.49	(0.68; 3.24)	0.31
Female Sex * Diabetes	0.54	(0.15; 2.02)	0.36
Female Sex * Creatinine	1.04	(0.27; 4.08)	0.95
Female Sex * PRS (continuous per SD)	0.93	(0.69; 1.24)	0.60

Table XIV: Cox regression model for prediction of CHD events evaluating the interaction of aspirin-treatment with the PRS

	HR	**95%**	**p-value**
PRS per SD change	1.25	(1.05; 1.50)	0.013
Randomization to Aspirin	0.70	(0.35; 1.40)	0.32
Interaction of PRS with “Randomization to Aspirin”	0.93	(0.71; 1.21)	0.58

Abbreviations: PRS = polygenic risk score, HR = hazard ratio, CI = confidence interval.

4. Supplemental Figures

Figure I: Study flow chart

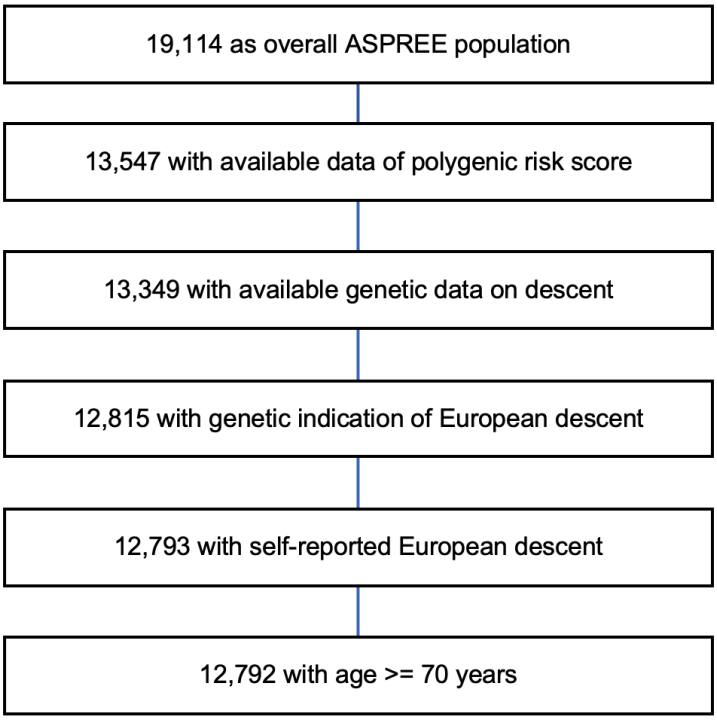
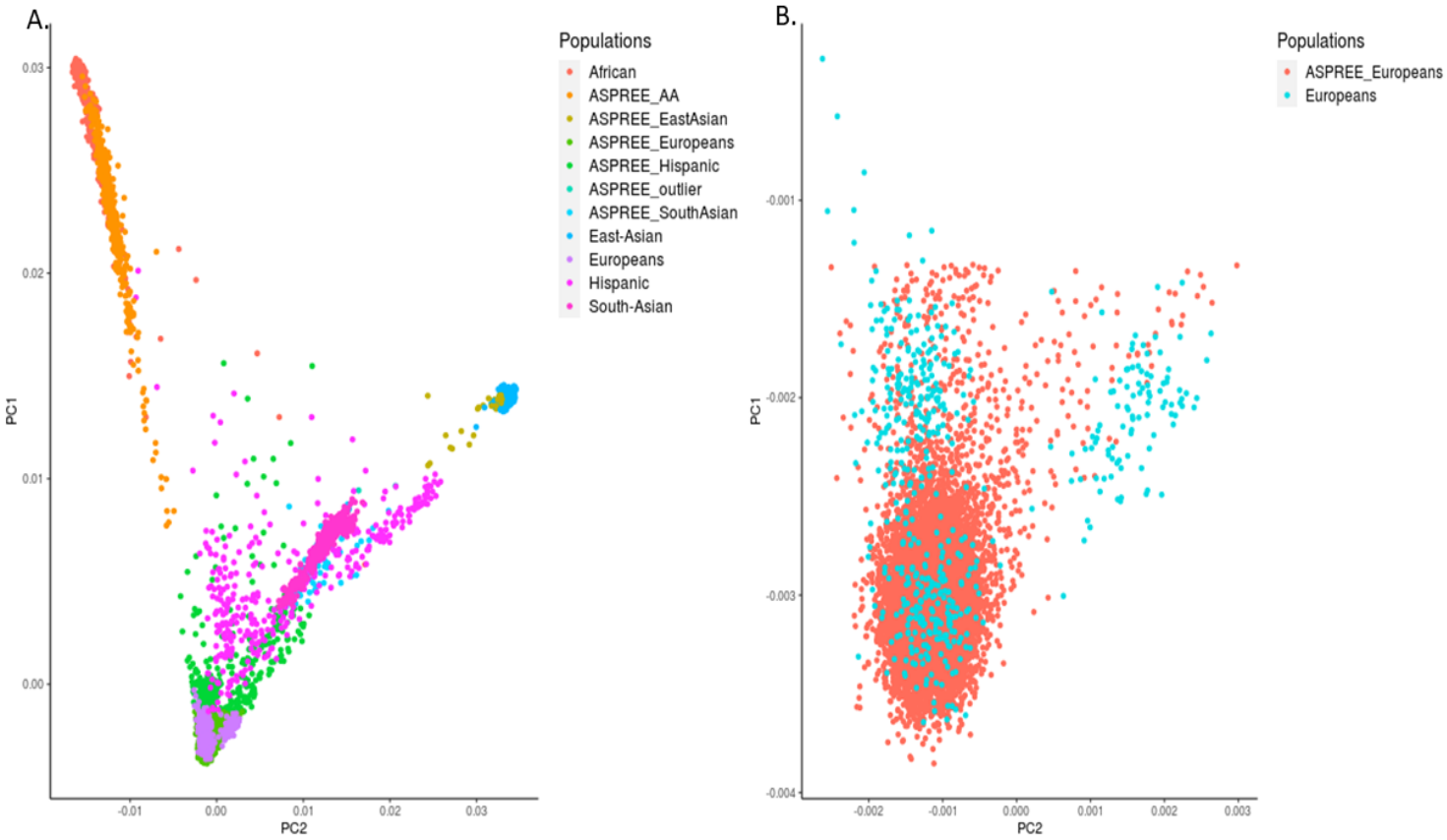
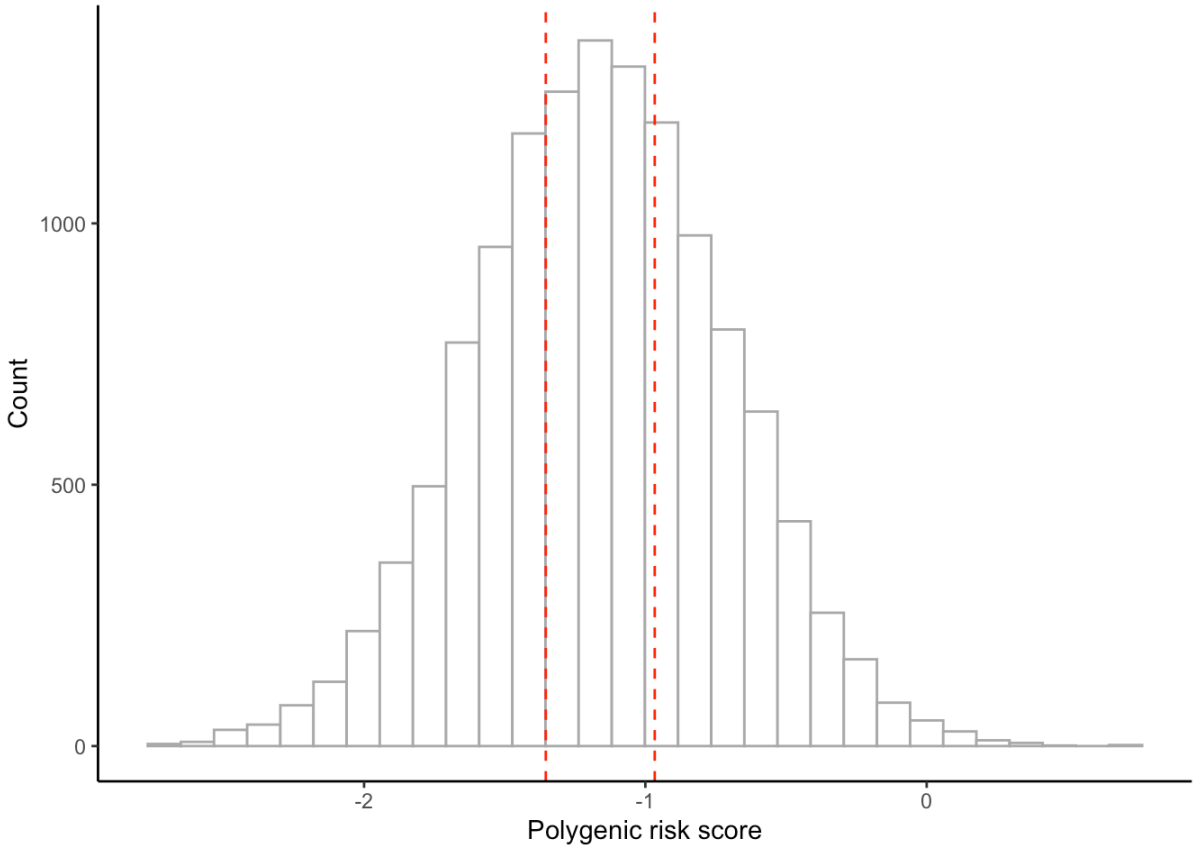


Figure II: Principal component analysis (PCA) of the ASPREE cohort compared with the 1000 Genome Project. A. Shows PCA plot of all ASPREE participants mapped with 1000 Genome populations. B. Shows PCA plot of ASPREE Europeans samples with 1000 Genome Europeans samples that were included in this study.



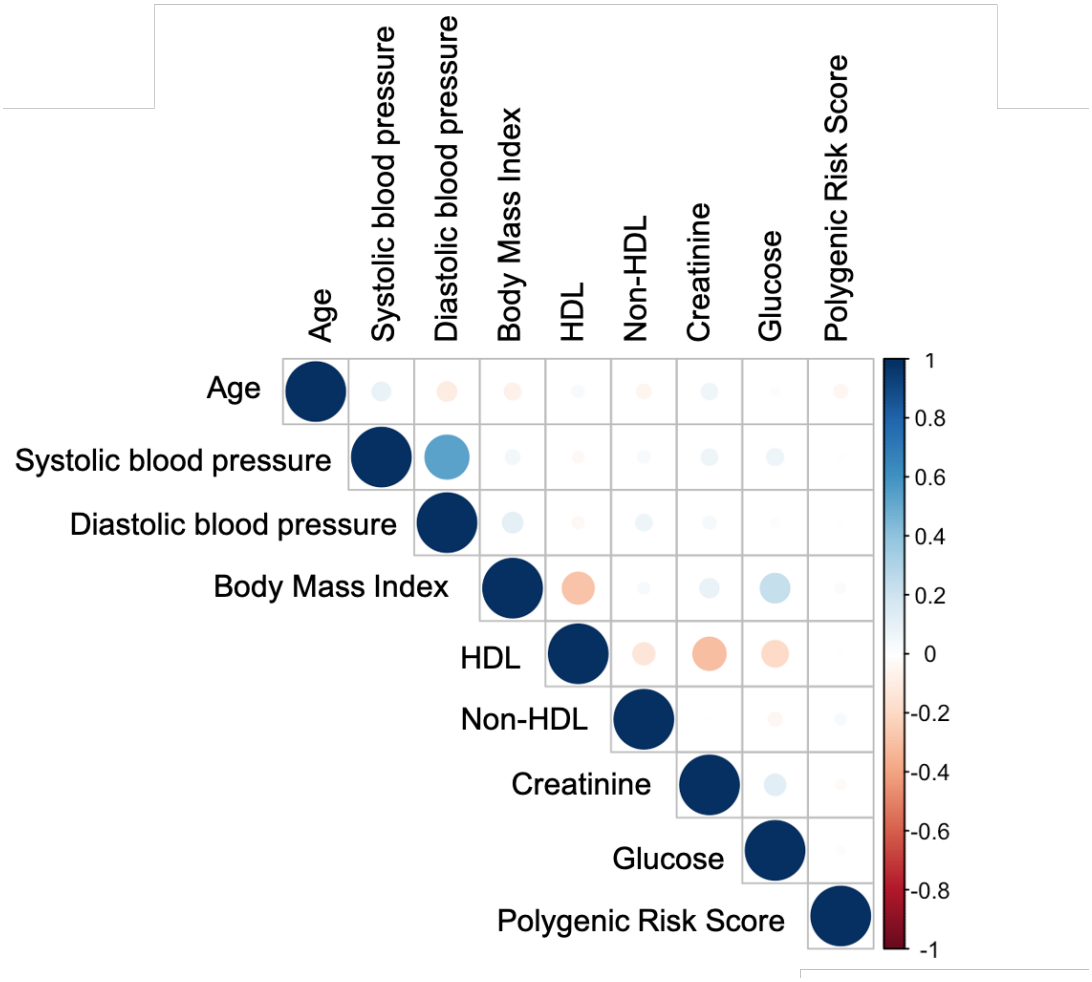
In Figure legend 1000 genome populations are: Europeans, South Asians, East Asians, African American and Hispanics. ASPREE_AA is African American samples.

Figure III: Distribution of the Polygenic Risk Score in the study population



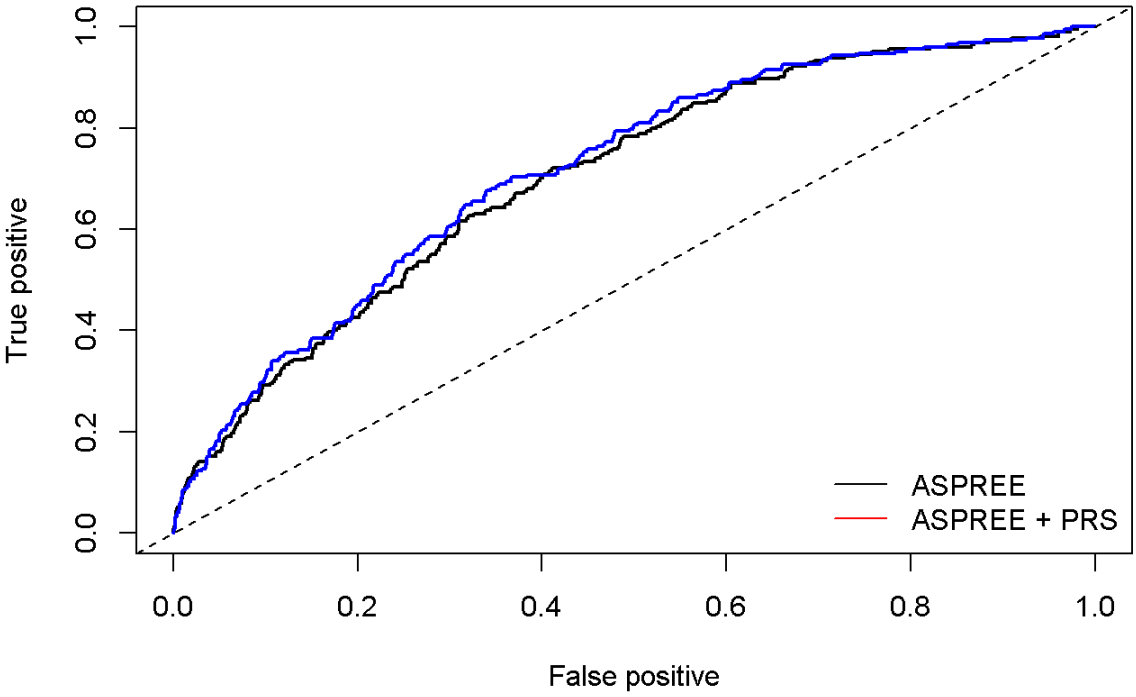
The distribution of the PRS in the study population is provided. The mean value was -1.16 (SD 0.45). The red dashed lines indicate the PRS tertiles. The first tertile ranged from -2.73 to < -1.35, the second tertile ranged from 1-35 to < -0.97 and the third tertile ranged from -0.97 to 0.69.

Figure IV: Correlation matrix of continuous variables including the Polygenic Risk Score



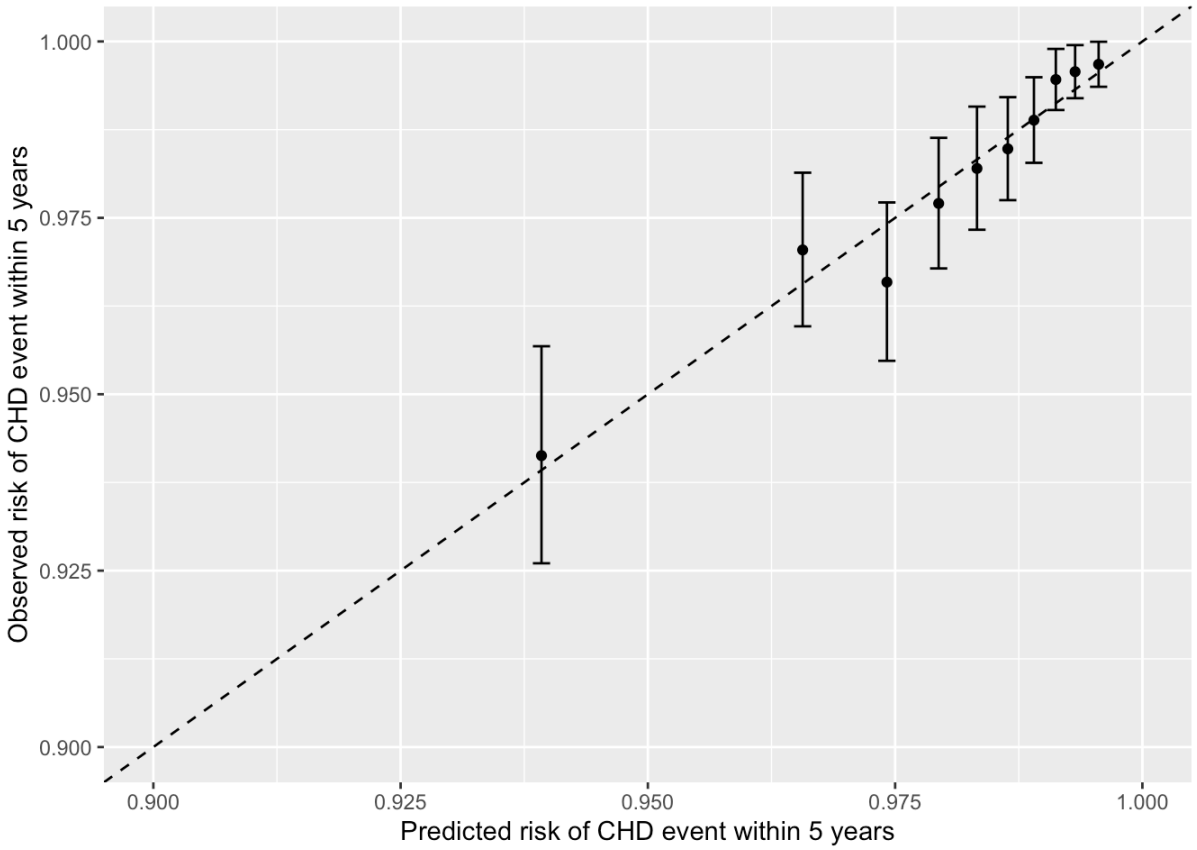
A correlation matrix including only continuous variables is provided. The size and the color of the circles indicate the strength of correlation, ranging from r = -1 (red) to +1 (blue).

Figure V: AUC for the conventional model and after addition of the PRS to the conventional model



The area under the curve is provided for the conventional model including age, sex, smoking status (current smoking versus former or never smoking), systolic blood pressure, non-HDL, HDL, diabetes and creatinine. In addition, the area under the curve is re-calculated after adding the PRS to the risk model to discriminate between CHD events and non-events.

Figure VI: Calibration of the conventional model + continuous PRS



In this figure the observed and predicted risk for CHD events is compared.