Table 1. Characteristics of study participants from the FOS (N=3,660) and UKB (N=327,837) Characterisitics for individuals in the Framingham Offspring Study (FOS) and UK biobank reported here.

	FOS (N=3,660)	**UKB (N=327,837)**
Age at risk estimation, mean (SD), years	35.9 (10.3)	56.1 (8.1)
Female, n (%)	1,843 (50.4)	186,507 (56.9)
White, n (%)	3,588 (100)	274,927 (83.9)
Incident CAD, n (%)	746 (21)	11190 (3.4)
Follow-up period, mean (SD)		12.1 (1.9)
Age at CAD, mean (SD), years	71.2 (12.2)	66.3 (7.2)
Type 1 or 2 Diabetes mellitus, n (%)	37 (1)	2413 (0.7)
Current smoking, n (%)	1612 (44.0)	33869 (10.3)
Total cholesterol, mean (SD), mg/dL	198.5 (39.2)	228.6 (41.4)
HDL Cholesterol, mean (SD), mg/dL	51.9 (16.0)	57.2 (14.8)
LDL cholesterol, mean (SD), mg/dL	127.3 (37.2)	144 .0 (31.9)
Triglycerides	99.1 (86.7)	151.9 (90.3)
Diastolic blood pressure, mean (SD), mmHg	78.9 (10.5)	82.8 (11.2)
Systolic blood pressure, mean (SD), mmHg	121.8 (16.5)	139.7 (20.4)
Taking antihypertensive medication, n (%)	122 (3.3)	41,088 (12.5)
PCE 10-year risk category		
Low or borderline (<7.5%), n (%)	-	207,150 (63.2)
Intermediate (≥7.5 to <20%), n (%)	-	96,775 (29.5)
High (≥20%), n (%)	-	23,912 (7.3)
Genetic data available, n (%)	2,656 (72.5)	327,837 (100.0)
CAD polygenic score category		
Low, n (%)	531 (20.0)	65,696 (20.0)
Intermediate, n (%)	1,593 (60.0)	196,750 (60.0)
High, n (%)	532 (20.0)	65,391 (19.9)
Race (% White)	0 (0.0)	274,927 (83.8%)

Figure Titles and Legends

Figure 1. Dynamic Hazard Ratio of CAD for Genomic and Nongenomic Risk Factors by Age at Estimation

The age-specific hazard ratio (HR) for lifetime risk of coronary artery disease is plotted for multiple risk factors at each age of enrollment (A) between 18 and 57 years in the Framingham Offspring Cohort (N=3,660), and (B) between 40 and 70 years in the UK Biobank (N=327,837). The HR for all risk factors are dynamic over the life course with a general age-dependent decline. The HR is obtained from Cox proportional hazards estimate at each age of enrollment for a standardized unit increase in each of polygenic score, total cholesterol, HDL cholesterol, and systolic blood pressure or a binary indicator for smoking and diabetes mellitus (only in the UK Biobank given the low incidence of DM in this population).No covariates are used in the analysis to isolate the effect of each covariate separately.

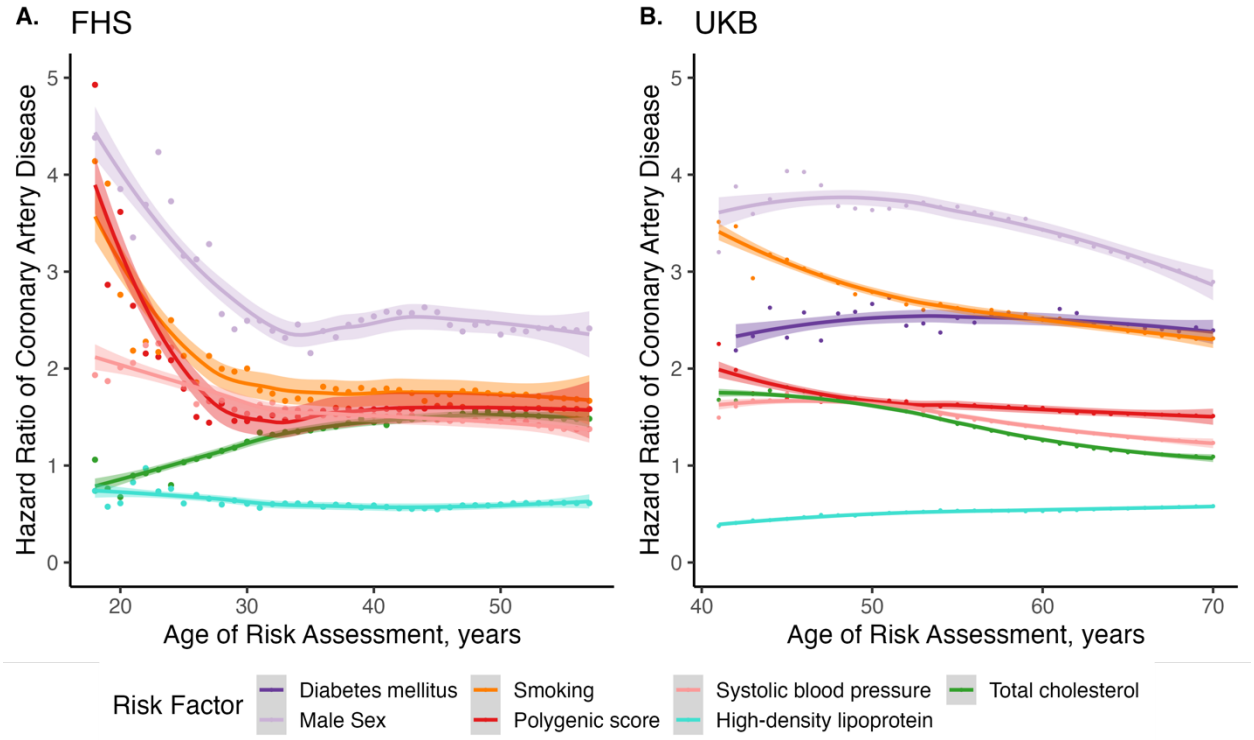

Figure 2. Proportion of Variation Explained by Different Genomic and Nongenomic CAD Risk Factors by Age at Estimation

The proportion of variation explained (PVE) by multiple risk factors is plotted at each age of enrollment (A) between 18 and 57 years in the Framingham Offspring Cohort (N=3,660), and (B) between 40 and 70 years in the UK Biobank (N=327,837). The PVE was obtained from McFadden's Pseudo R2 from a logistic regression model estimating the effect of each risk factor on the development of coronary artery disease for individuals up to and including the age along the X axis. Each model is fit in a univariate without any additional covariates consistent with Fig 1.

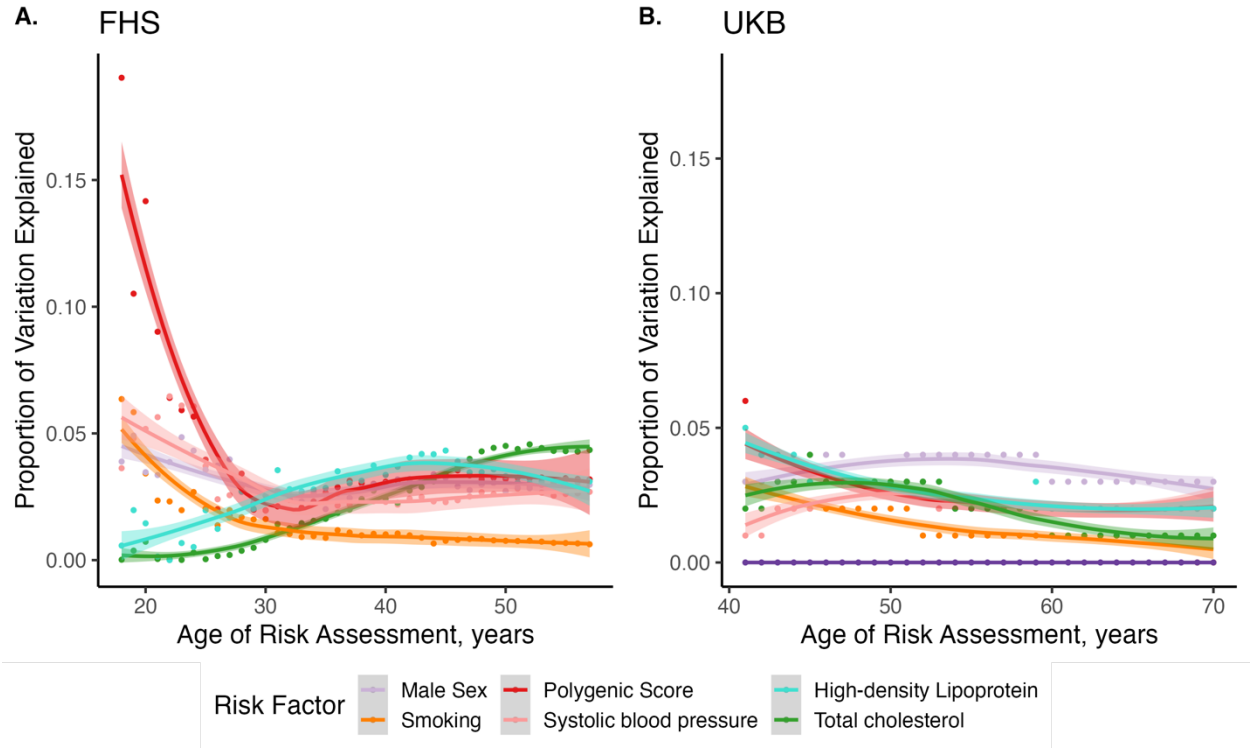

Figure 3. Absolute and Relative Incidence Rate of Genomic and Nongenomic Risk by Age Group

In the UK Biobank (N=327,837), three age groups (<55, 55-65, and >65 years) at risk estimation were used to compare the stratification of the observed absolute and relative risk across gradients of the genomic (polygenic score percentile) and nongenomic (PCE 10-year risk estimate) predictors. (A) The absolute risk of CAD increased with increased with increasing polygenic score percentile in all three age groups, and older participants had higher absolute risk of CAD. From the 1st to the 99th percentile, the absolute risk of CAD ranged from 0.7 to 3.9% in the <55 years age group, 1.9 % to 7.0 % in the 55-65 years age group, and 3.3 to 10.4% in the >65 years age group. (B) The polygenic score distribution was similar across three age groups. (C) However, when we evaluate the relative risk of CAD across the gradient of polygenic risk compared to the 1st percentile, younger individuals had the highest relative risk. The 99th percentile of polygenic score was associated with a 5.2-fold increase in risk in the <55 years age group, 3.6-fold increased risk in the 55-65 years age group, and 3.2-fold increase in risk in the >65 years age group.

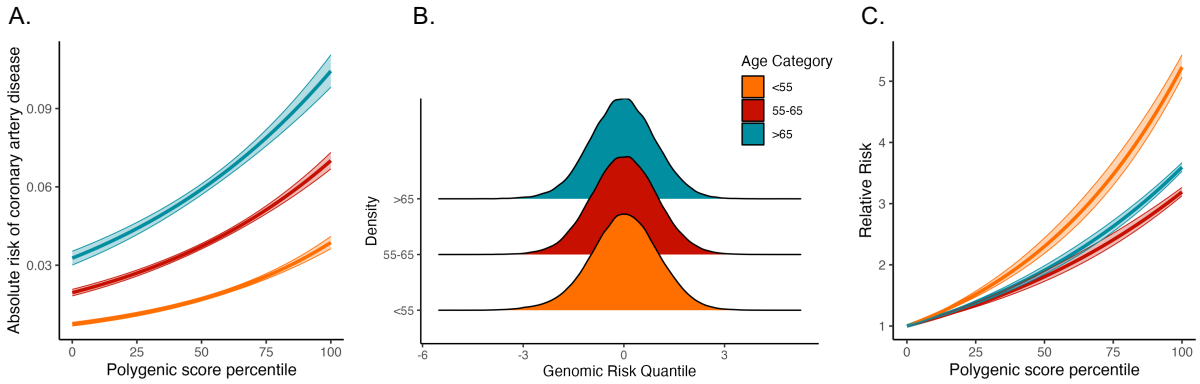

Figure 4. Cumulative Hazard curve by PRS and PCE quintile for each age group.

In the UK Biobank, N=327,837, we stratify by age into three groups: those <55, 55-65 and over 65 at enrollment. Within each group we further stratify by age-group specific PRS and PCE rank categories defined as lowest 20%, 20-80% and top 20%. We report the cumulative hazard over the follow up time (median 12.2 years).

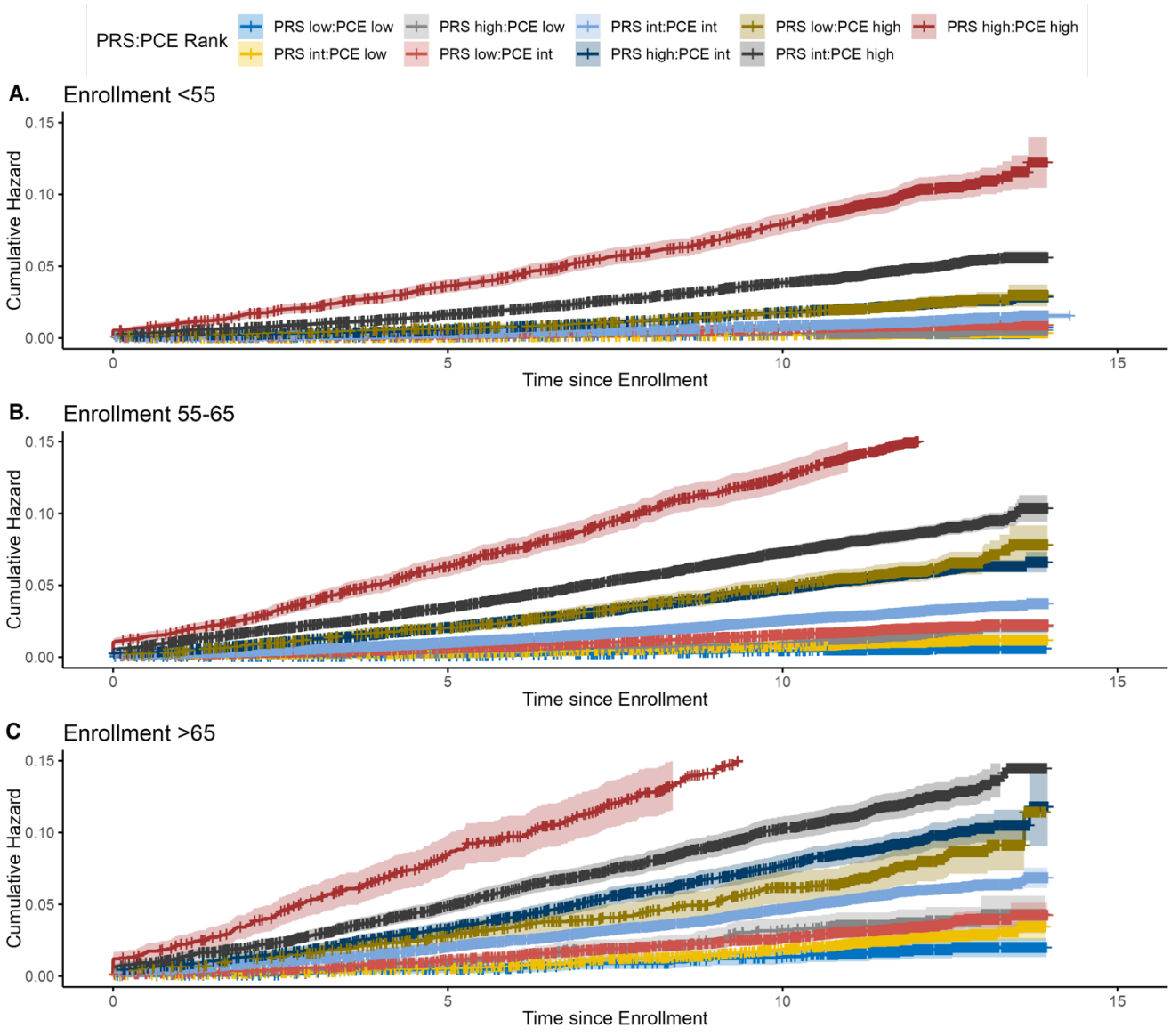

Figure 5. Earlier Events Predicted by PRS

In the UK Biobank (N=327,837) and for all ages of enrollment we consider the mean age of event (yweA) by overall PRS or PCE decile.

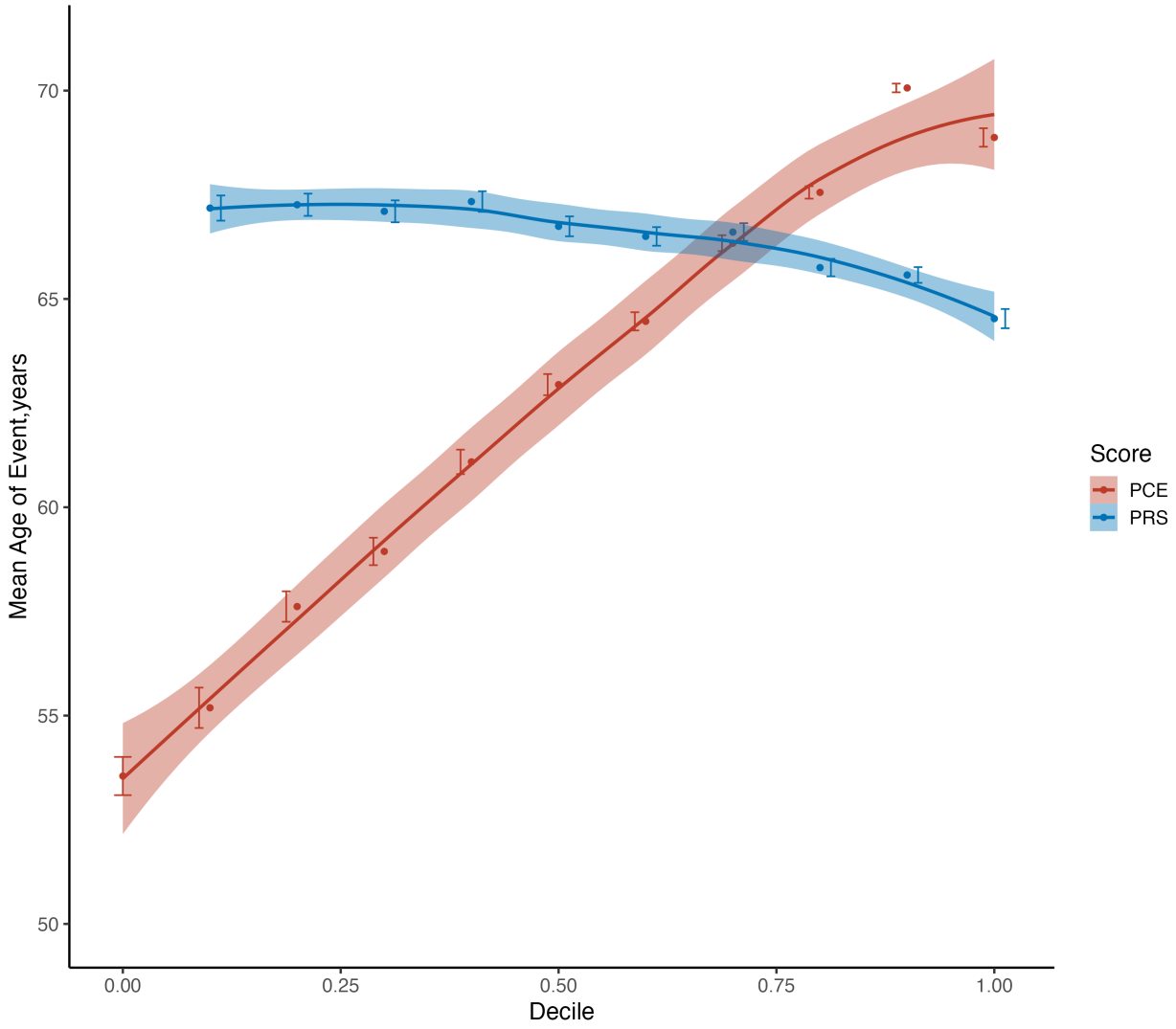

Figure 6. Proportion of Cumulative CAD events predicted by genomic and clinical risk estimation by age of estimation

In the UK Biobank (N=327,837) and for individuals in 5-year age strata between 40 and 75 years at time of risk estimation, we plot the proportion of cumulative CAD events predicted using high genomic risk (polygenic score in the top quintile), high clinical risk (PCE 10-year risk ≥7.5%) or both at enrollment. We specify high clinical risk as >7.5% in line with clinical criteria for younger individuals[1,2] With increasing age, the proportion of lifetime CAD events predicted by genomic risk decreased and that predicted by nongenomic risk increased. At younger ages (40-45 years), 32.3% of cumulative CAD events occurring in this age group were predicted by high polygenic score alone compared to only 9.1% by high PCE alone. Conversely at older ages (65-70 years), only 1.3% of CAD events occurring in this age group were predicted by a high polygenic score at enrollment alone compared to 68.3% by high PCE alone.

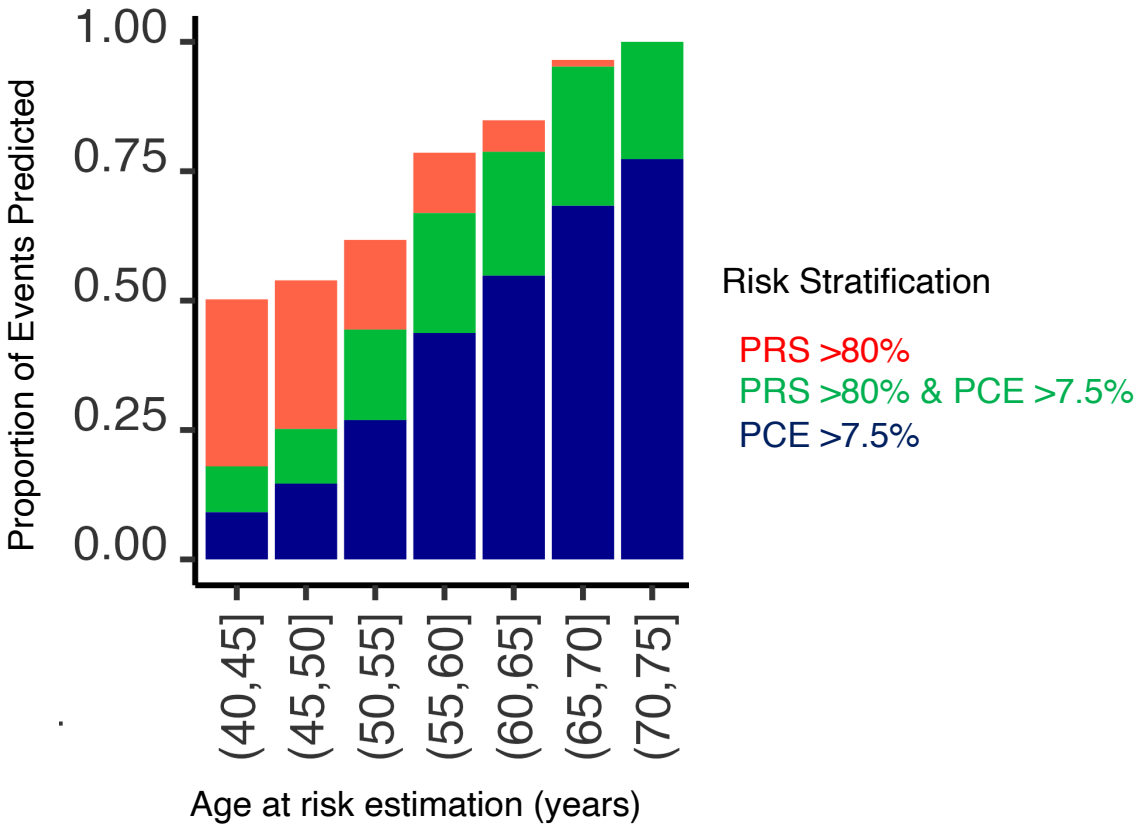

Figure 7: Describing Events over the Lifecourse

In the UK Biobank (N=327,837) we stratify all individuals by criterial at baseline and consider their cumulative hazard of CAD diagnosis by time of event with age as time scale as in [1–3].

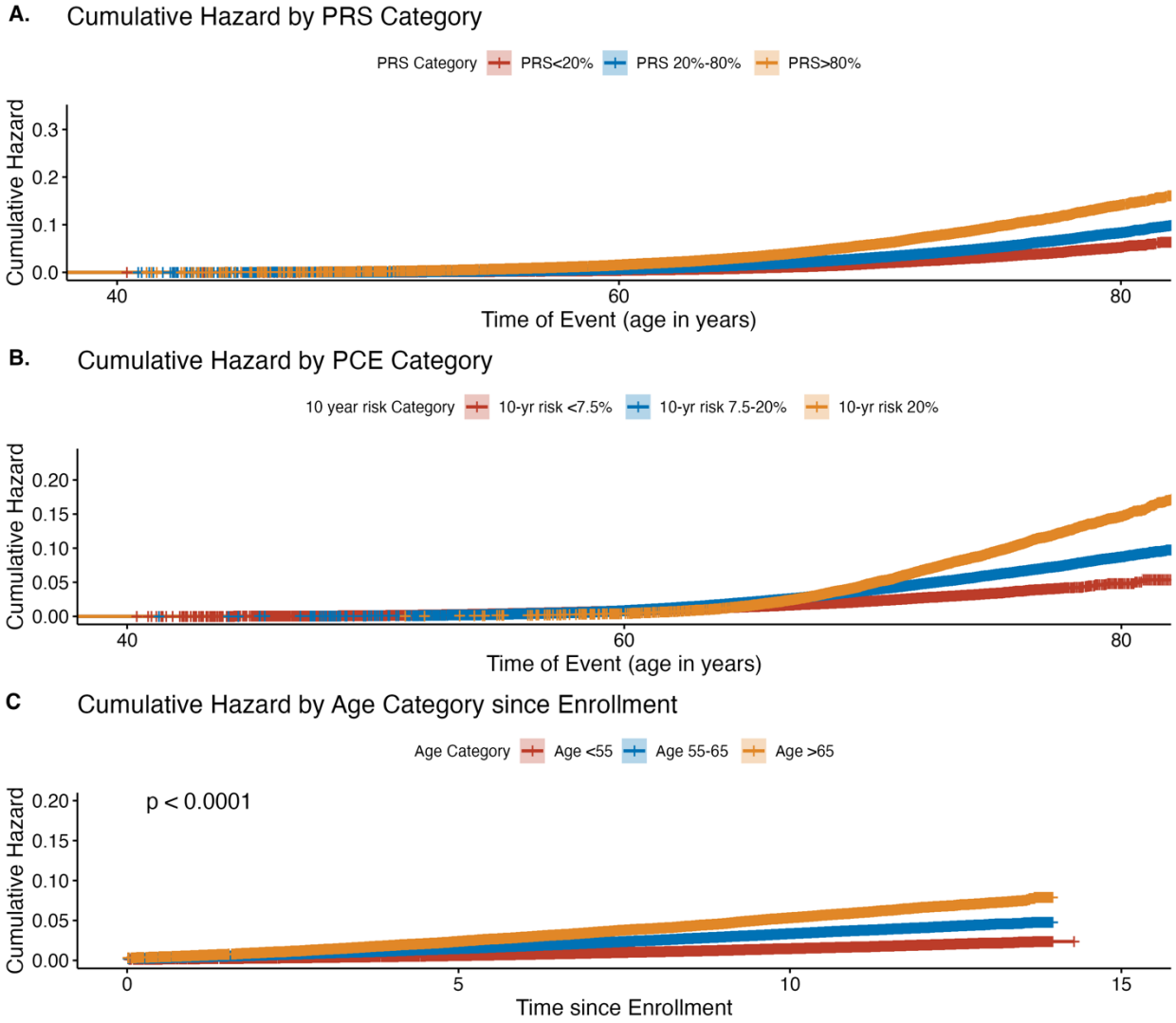

Figure 8. Performance of integrated genomic and nongenomic risk models for CAD by age of estimation

In the UK Biobank (N=327,837), the Area Under the Receiver Operator Curve (AUC) is shown from a logistic regression for the effect of high genomic risk (polygenic score in the top quintile), high nongenomic risk (PCE 10-year risk ≥20%), or both on development of CAD for individuals in 5-year age strata between 40 and 75 years at of risk estimation. The AUC for genomic risk model is higher than nongenomic risk model under age 50 years. The inverse is true after age 50 years whereby the nongenomic model outperforms the genomic model. An integrated model including both genomic and nongenomic factors outperforms either model alone throughout the life course and has the highest increment in AUC to either model at younger ages.