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ORIGINAL ARTICLE

Dynamic Importance of Genomic and Clinical Risk for Coronary Artery Disease Over the Life Course

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BACKGROUND: Earlier identification of high coronary artery disease (CAD) risk individuals may enable more effective prevention strategies. However, existing 10-year risk frameworks are ineffective at earlier identification. We sought to understand how the variable importance of genomic and clinical factors across life stages may significantly improve lifelong CAD event prediction.

METHODS: A longitudinal study was performed using data from 2 cohort studies: the FOS (Framingham Offspring Study) with 3588 participants aged 19 to 57 years and the UKB (UK Biobank) with 327 837 participants aged 40 years to 70 years. A total of 134 765 and 3 831 734 person-time years were observed in FOS and UKB, respectively. Hazard ratios for CAD were calculated for polygenic risk score (PRS) and clinical risk factors at each age of enrollment. The relative importance of PRS and pooled cohort equations in predicting CAD events was also evaluated by age groups.

RESULTS: The importance of CAD PRS diminished over the life course, with a hazard ratio of 3.58 (95% CI, 1.39–9.19) at the age of 19 years in FOS and a hazard ratio of 1.51 (95% CI, 1.48–1.54) by the age of 70 years in UKB. Clinical risk factors exhibited similar age-dependent trends. PRS significantly outperformed pooled cohort equations in identifying subsequent CAD events in the 40- to 45-year age group, with 3.2-fold more appropriately identified events. Overall, adding PRS improved the area under the receiving operating curve of the pooled cohort equations by an average of +5.1% (95% CI, 4.9%–5.2%) across all age groups; among individuals <55 years, PRS augmented the area under the receiver operater curve (ROC) of the pooled cohort equations by 6.5% (95% CI, 5.5%–7.5%; $P<0.001$).

CONCLUSIONS: Genomic and clinical risk factors for CAD display time-varying importance across the lifespan. The study underscores the added value of CAD PRS, particularly among individuals younger than 55 years, for enhancing early risk prediction and prevention strategies. All results are available at https://surbut.github.io/dynamicHRpaper/index.html.

Key Words: cardiovascular diseases ■ coronary artery disease ■ genomics ■ risk factors ■ statistics

Accurate risk estimation for coronary artery disease (CAD) early in the life course is a major goal in medicine, as CAD remains the leading cause of mortality and morbidity.[1] Because coronary atherosclerosis often begins early in life and progresses over the life course, early identification of high-risk individuals offers the possibility for substantial risk mitigation.[2]

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Nonstandard Abbreviations and Acronyms

CAD	coronary artery disease
FOS	Framingham Offspring Study
HR	hazard ratio
LDL	low-density lipoprotein
PCE	pooled cohort equations
PRS	polygenic risk score
UKB	UK Biobank

There are several reasons contemporary risk estimators in clinical practice do not adequately identify high-risk individuals early in life. First, guideline-based risk calculators are valid only for ages ≥40 years and are often limited to short-term (eg, 10-year) fixed-time horizons.[3,4] Therefore, chronologic age remains the primary determinant of estimated 10-year risk, and high risk cannot be identified earlier in life, thereby delaying effective prevention opportunities.[5] Second, even when prediction is extended to estimate lifetime risk, it fails to capture the dynamic trajectory of an individual's changing risk profile, such as changing biomarkers, biometric measurements, or lifestyle. Finally, models are developed assuming proportional hazards, which impose that the effect of each risk factor is either constant over the baseline hazard ratio (HR) through life or that interaction is a linear function of time. Both assumptions are inaccurate for CAD clinical risk factors.[6]

CAD polygenic risk score (PRS) has emerged as a tool to estimate risk complementary to clinical risk factors and is uniquely available early in life. Current modeling of clinical risk factors, as well as CAD PRS, typically use a fixed-time horizon and rely on assumptions that do not hold true for the dynamic landscape of CAD risk factors. Integrated modeling of both genomic and clinical risk factors in a single, dynamically adjusting model over the life course might provide a more accurate estimation of risk. Although recent work has shown that CAD PRS carries greater effects for younger people,[7] its comparative and complementary performance with clinical risk calculators is less clear for both premature and cumulative events across a broad age range. Furthermore, understanding the dynamic nature of fixed risk factors over the life course remains unexplored. Integrating genomic and clinical risk in a single model continues to be a barrier to the clinical implementation of CAD PRS at scale. Such integration will ideally incorporate the dynamic importance of genomic and clinical risk for CAD over the life course for optimal utility.

Here, we leverage 2 cohorts of individuals enrolled across the ages of 19 to 70 years and followed for up to 44 years to show that genomic and clinical risk factors vary in their importance over the life course and to explain a changing proportion of variation for CAD risk. We show that CAD PRS adds the most information for young and early middle-aged individuals when compared with older individuals and predicts a greater number of both premature and overall events for younger individuals. This framework mitigates current age-dependent limitations of CAD clinical risk scores.

METHODS

All codes necessary for reproduction of these results have been made publicly available on github and can be accessed at https://surbut.github.io/dynamicHRpaper/index.html. Informed consent was obtained from all participants, and secondary data analyses of dbGAP (data-base of genotypes and phenotypes) -based FOS (Framingham Offspring Study) and UKB (UK Biobank) were approved by the Mass General Brigham Institutional Review Board applications 2016P002395 and 2021P002228. All data from the UKB (https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access) are made available to researchers from universities and other institutions with genuine research inquiries after institutional review board and UKB approval. All data from the FOS are made available from dbGap (https://www.ncbi.nlm.nih.gov/gap/) to researchers from universities and other institutions with genuine research inquiries after institutional review board approval. All data generated during this study are included in this published article and its Supplemental Material. All methods are now available as Supplemental Material only.

RESULTS

Study Participants

We studied 2 cohorts free of cardiovascular disease at baseline and spanning the life course: (1) FOS comprising 3588 individuals (50.9% female) ages 19 to 50 years at enrollment and followed for a median of 43.7 years (interquartile range, 38.7–47.4 years) and (2) UKB, comprising 327 837 participants (57% female) ages 40 to 70 years at enrollment followed for a median of 12.1 years (interquartile range, 11.4–12.7 years; Table). Apart from smoking, clinical risk factors were more prevalent in the UKB as expected given older age compared with FOS. For example, 1581 (44%) FOS participants (enrolled 1971–1975) were current smokers, compared with 33 869 (10%) UKB participants (enrolled 2006–2010). During follow-up, 695 (19.4%) FOS participants and 11 190 (3.4%) UKB participants developed CAD. Of those incident events, the proportion of premature CAD events—defined as occurring before the age of 55 years—were 179 of 695 (25.8%) in the FOS and 1085 of 11 190 (9.7%) in the UKB, respectively.

Age-Dependent Effects of Genomic and Clinical Risk Factors

We calculated the HR of CAD per SD of PRS at each age of enrollment. The HR per SD of CAD PRS decreased over the life course—from 3.58 (95% CI, 1.39–9.19) at

Table. Characteristics of Study Participants From the FOS (N=3588) and UKB (N=327 837)

Characteristics	FOS (N=3588)	UKB (N=327 837)
Age at risk estimation, y, mean (SD)	35.9 (10.2)	56.1 (8.1)
Female, n (%)	1828 (50.9)	186 507 (56.9)
White race, n (%)	3588 (100)	274 927 (83.9)
Incident CAD, n (%)	695 (19.3)	11 190 (3.4)
Follow-up period, median (IQR)	43.7 (38.7–45.3)	12.1 (11.4–12.7)
Diabetes, n (%)	27 (0.7)	2413 (0.7)
Current smoking, n (%)	1581 (44.1)	33 869 (10.3)
Total cholesterol, mg/dL, mean (SD)	197 (38.8)	228.6 (41.4)
HDL cholesterol, mg/dL, mean (SD)	52.1 (16.0)	57.2 (14.8)
LDL cholesterol, mg/dL, mean (SD)	127 (36.6)	144.0 (31.9)
Triglycerides, mg/dL, mean (SD)	99.1 (86.7)	151.9 (90.3)
Diastolic blood pressure, mg/dL, mean (SD)	78.5 (10.9)	82.8 (11.2)
Systolic blood pressure, mg/dL, mean (SD)	121 (16.4)	139.7 (20.4)
Taking antihypertensive medication, n (%)	102 (2.8)	41 088 (12.5)
PCE 10-year risk category		
Low or borderline (<7.5%), n (%)	…	207 150 (63.2)
Intermediate (≥7.5–<20%), n (%)	…	96 775 (29.5)
High (≥20%), n (%)	…	23 912 (7.3)
Genetic data available, n (%)	2656 (72.5)	327 837 (100.0)
CAD polygenic risk score category		
Low, n (%)	531 (20.0)	65 696 (20.0)
Intermediate, n (%)	1593 (60.0)	196 750 (60.0)
High, n (%)	532 (20.0)	65 391 (20.0)

Characteristics for study participants from the FOS and UKB are reported for all individuals based on data obtained at enrollment. CAD indicates coronary artery disease; FOS, Framingham Offspring Study; HDL, high-density lipoprotein cholesterol; IQR, interquartile range; LDL, low-density lipoprotein cholesterol; PCE, pooled cohort equations; and UKB, UK Biobank.

age 19 years to 1.99 (95% CI, 1.06–3.70) at age 56 years in FOS and from 2.25 (95% CI, 1.77–2.87) at age 41 years to 1.39 (95% CI, 1.30–1.48) by the age of 70 years in UKB (Figure 1; Tables S1 and S2).

In Figure 1A, the model suggests high cholesterol is protective at the youngest age range and is then associated with increasing risk from mid-20s to 40. We note that the use of FOS allowed us to consider a wider age range; however, this cohort also was followed over a different period of study (enrolled starting in the year 1971). Although we excluded individuals on lipid-lowering medication at baseline (only 22 individuals), FOS enables longitudinal follow-up of lipid-lowering medications initiated over time. Analysis of this data reveals that individuals who enrolled very young (eg, age <25 years) were not followed long enough to reach ages where statin prescription prevalence would increase substantially and potentially attenuate the risk of high LDL (low-density lipoprotein) cholesterol, but individuals who enrolled at older ages (>50) reached American College of Cardiology/American Heart Association elevated risk before the availability of statin medications (circa 1990). Individuals between ages 30 and 40 showed peak ultimate use of statins during the study period, which attenuated the effects of elevated cholesterol, thereby reducing the HR (Figure S4).

We next calculated the HR of clinical risk factors at each age of enrollment and similarly observed decreasing HRs over the life course. For example, the HR (95% CI) of CAD for smoking decreased from 1.98 (0.44–8.84) at the age of 19 years to 0.98 (0.41–2.33) at the age of 56 years in the FOS and from 3.51 (2.13–5.80) at the age of 41 years to 1.62 (1.28–2.04) at the age of 70 years in the UKB. The trends were similar for systolic blood pressure and diabetes (Figure 1; Tables S1 and S2). Excess risk associated with male sex similarly declined with age—from 3.29 (95% CI, 0.64–16.95) at the age of 19 years to 2.59 (95% CI, 0.92–7.25) at the age of 57 years in the FOS and from 3.20 (95% CI, 1.82–5.64) at the age of 41 years to 1.99 (95% CI, 1.74–2.26) at the age of 70 years in the UKB (Figure 1; Tables S1 and S2).

We next computed the proportion of variation explained of CAD on each risk factor for individuals up to and including the age in question. We observed a decreasing proportion of variation explained with increasing age for PRS, from 19% (95% CI, 18.9–19.1) at the age of 19 years to 3.2% (95% CI, 3.19–3.21) at the age of 57 years in the FOS and from 5.9% (95% CI, 5.89–5.91) at the age of 40 years to 1.7% (95% CI, 1.69–1.71) at the age of 70 years (Figure S5; Tables S3 and S4).

Relative Importance of Genomic and Clinical Risk of CAD by Age

To compare the relative importance of genomic versus clinical risk, we limited our analysis to the UKB where both could be calculated. In contrast to pooled cohort equations (PCE), the distributions of PRS of participants across all age groups were similar and the absolute risk of CAD increased with increasing PRS (Figure 2A and 2B; Figures S6 and S7). Over the study period, the absolute CAD risk difference between those <55 years in the first and 99th percentiles was 3.1%, whereas at >65 years rose to 7.1% (Figure 2A). However, the corresponding relative risks were 5.2-fold (95% CI, 5.1–5.4) and 3.2-fold (95% CI, 3.1–3.3), respectively (Figure 2C). We observe similar trends in absolute risk by using sex-specific analyses (Figures S8 and S9), although we note that the steeper relative risk in younger ages is less apparent in males.

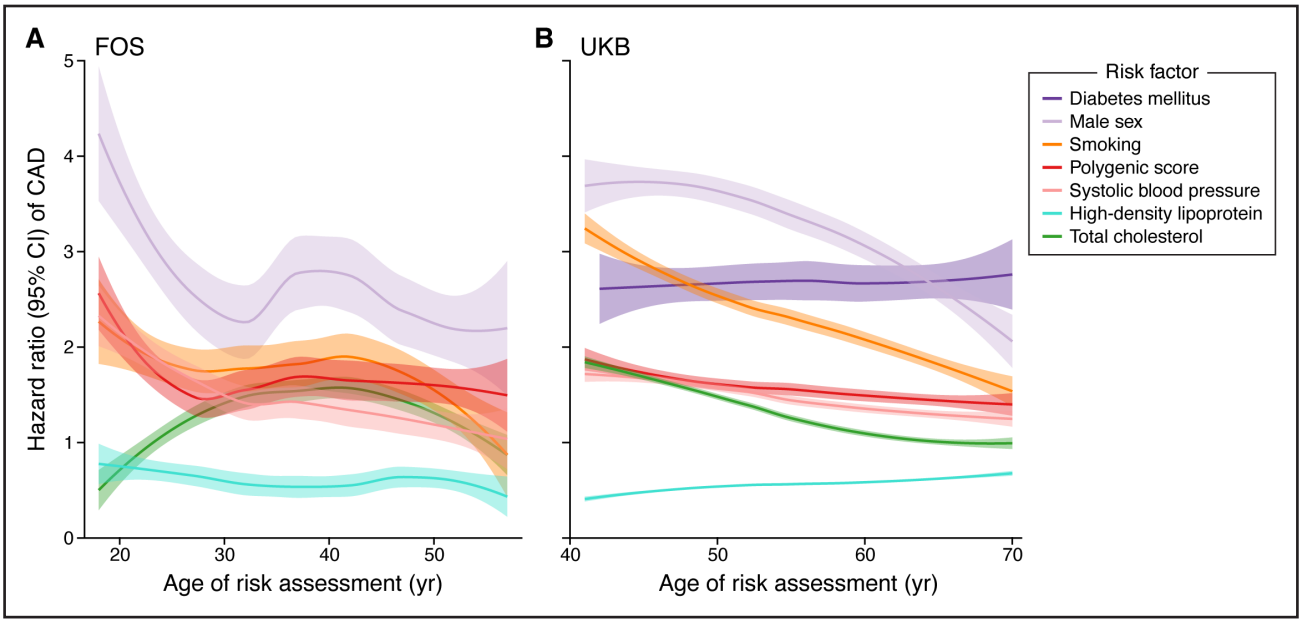

Figure 1. Dynamic hazard ratio of coronary artery disease (CAD) for genomic and clinical risk factors by age at estimation. The age-specific hazard ratio (HR) for risk of CAD is plotted for multiple risk factors at each age of enrollment (**A**) between 19 and 57 years in the FOS (Framingham Offspring Study; N=3588) and (**B**) between 40 and 70 years in the UKB (UK Biobank; N=327 837). The HR is obtained from Cox proportional hazards estimate at each age of enrollment for a standardized unit increase in each polygenic score, total cholesterol, HDL (high-density lipoprotein) cholesterol, and systolic blood pressure or a binary indicator for smoking, male sex, and diabetes (only in the UKB given the low prevalence of diabetes in FOS). No covariates are used in the analysis to isolate the effect of each risk factor separately.

One might expect that individuals free of CAD at enrollment (our study population) should be depleted, particularly at older age, in high PRS, and thus scaling to the general population should reveal this bias should it exist. However, both QQ plots and density histograms (Figure 2B) with and without principal component (PC) adjustment demonstrated no differences between PRS distributions among age categories, within the subset or general population (Figure S10).

When classifying PCE and PRS strata within each age group as high (top quintile), intermediate (middle 3 quintiles), and low (bottom quintile; Figure S11; Table S5), there was a marked gradient of cumulative hazard of CAD events over the 12-year follow-up period (Figure 3). This stratification was highest in the <55 years age group, ranging from 0.045% (95% CI, 0.23–0.67) for individuals with low PRS and low PCE to 14.6% (95% CI, 12.8–15.5) for individuals with high PRS and high PCE. The corresponding stratification in the >65 years age group was 4.6% (95% CI, 0.01–0.09) to 37.6% (95% CI, 0.11–0.64; Figure 3).

We then compared the ability of a high PRS versus high PCE in predicting CAD events across different age groups (Figure 4A). At younger ages of enrollment (40–45 years), high PRS predicted over 3.5-fold more events compared with high PCE—32.3% (95% CI, 32.0–32.5) of CAD events occurring in this age group were predicted by high PRS alone compared with only 9.1% (95% CI, 9.0–9.2) by high PCE alone.

Prediction of Premature CAD Events

Individuals with high PRS developed CAD earlier in life (mean 65.3 [95% CI, 65.0–65.5] years), whereas the average age of first CAD among the high PCE group was 70.8 (95% CI, 70.6–71.0) years (Tables S7 and S8). Mean age of CAD event decreased with increasing PRS, from 67.2 (95% CI, 66.6–67.8) years in the lowest decile to 64.5 (95% CI, 64.1–65.0) years in the highest decile. Conversely, individuals in the highest PCE decile had events 13.7 years later in life than those of the lowest PCE (Figure 4B; Table S9; Figure S11). Among individuals with CAD events occurring at <55 years, 427 (39.3%) had high PRS, but only 32 (2.9%) had high PCE. Because age is part of the PCE, this is not unexpected: individuals with higher PCE at enrollment will be older at enrollment and will therefore have later ages of events.

Augmenting Clinical Risk Models With Genomic Risk

Adding PRS to PCE augmented area under the curve across all ages but with the greatest impact in younger individuals (Figure 4C; Table S10). For individuals <55 years, the improvement was 6.3% (95% CI, 4.8–7.8) compared with only 2.9% (95% CI, 2.2–3.8) for those over 55 years. Furthermore, the area under the curve increased by 8.8% (95% CI, 8.4%–9.2%) in the 40- to 44-year age group, 7.8% (95% CI, 7.6%–8.0%) in

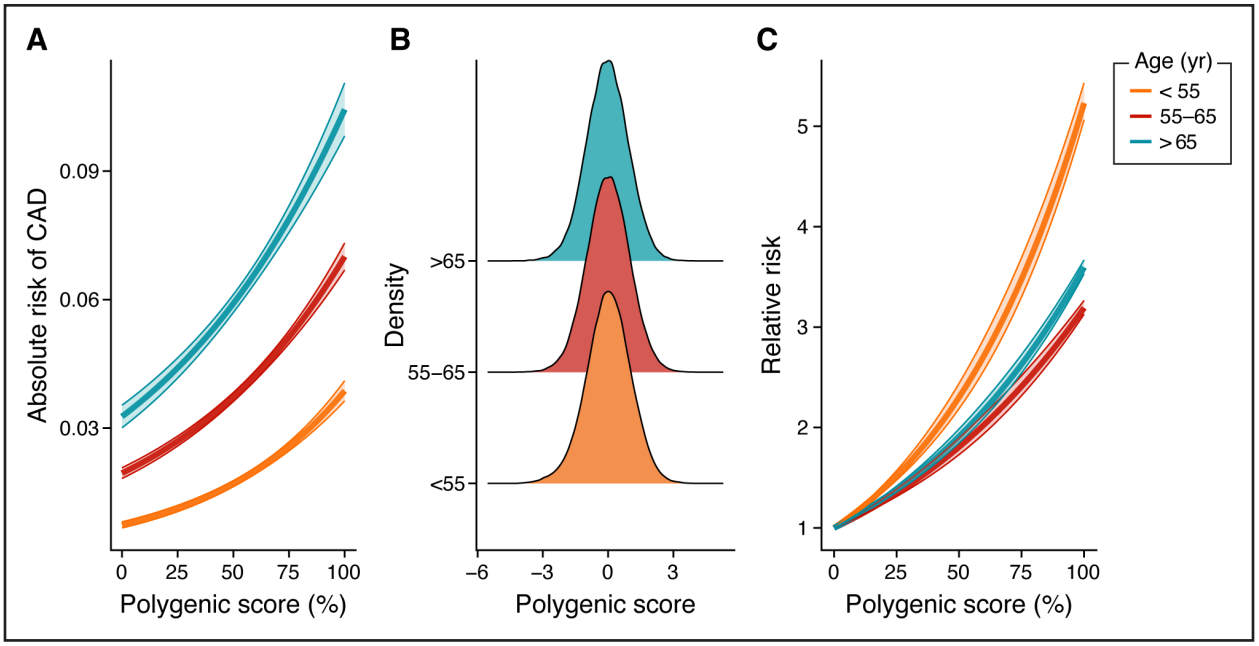

Figure 2. Absolute and relative incidence rate of coronary artery disease (CAD) by genomic risk per age group. In the UK Biobank (N=327 837), 3 age groups (<55, 55–65, and >65 years) at risk estimation were used to compare the stratification of the observed absolute and relative risk across polygenic score percentile. **A**, The absolute risk of CAD increased with increasing polygenic score percentile in all 3 age groups, and older participants had higher absolute risk of CAD. Absolute risk of CAD ranged from 0.7% to 3.9% in the <55 years age group, from 1.9% to 7.0% in the 55–65 years age group, and from 3.3% to 10.4% in the >65 years age group. **B**, The polygenic score distribution was similar across 3 age groups. **C**, Relative risk gradient of genomic risk is greatest for younger age groups. 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 increase in risk in the 55–65 years age group, and 3.2-fold increase in risk in the >65 years age group.

the 45- to 49-year group and 4.9% (95% CI, 4.7%–5.1%) in the 50- to 55-year age group, respectively (Figure 4C). The net proportion of CAD cases correctly reclassified by genomic risk (high PRS) was the highest in younger participants (16.1% for age <50 years and 3.4% for age <55 years) but receded for those over 55 years. The net proportion of controls correctly reclassified by genomic risk (low PRS) was the highest at older ages (15.1% at age <75 years) but diminishes in utility for those younger than 60 years (Figure S12; Table S11).

DISCUSSION

Our findings enhance our understanding of CAD risk factors by illustrating their dynamic importance throughout life. Unlike traditional models that operate under the constraints of fixed windows of time and proportional hazards, our work goes beyond these limitations to embrace the time-varying nature of these risk factors. The ability to track this dynamic trajectory provides new granularity in risk assessment, particularly for younger individuals. Our approach not only reconciles the time-varying impact of genomic and clinical risk factors but also highlights that CAD PRS offers value for risk assessment in individuals under 55 years over clinical risk factors alone.

Although current risk stratification emphasizes a focus on short-term risk, even an emphasis on a longer duration of risk fails to capture the dynamic trajectory of an individual's changing risk profile over time. A dynamic model of both genomic and clinical risk factors offers several practical implications. First, it is more accurate than existing risk calculators based on clinical risk factors alone. Second, it allows for more precise clinical risk stratification among younger individuals, for whom clinical risk factors perform poorly. Third, it supports the integration of genomics into clinical practice toward improved prevention of premature CAD events, which are generally missed by current clinical risk calculators.

HRs for conventional CAD risk factors and PRS are both age-dependent and challenge traditional modeling assumptions. This is important for consideration of risk across the life course beyond the present 10-year estimated risk framework, as recently highlighted in a National Heart Lung and Blood Institute workshop.[8] The Cox proportional hazards model has been the default approach for cardiovascular risk prediction, but its fundamental assumption—that the hazards in both groups compared are proportional—is often erroneous, and commonly reported HRs and risk estimates, such as the 10-year risk estimate from the PCE, are weighted averages of time-varying HRs.[9] Current risk calculators provide a fixed window estimate, as opposed to a

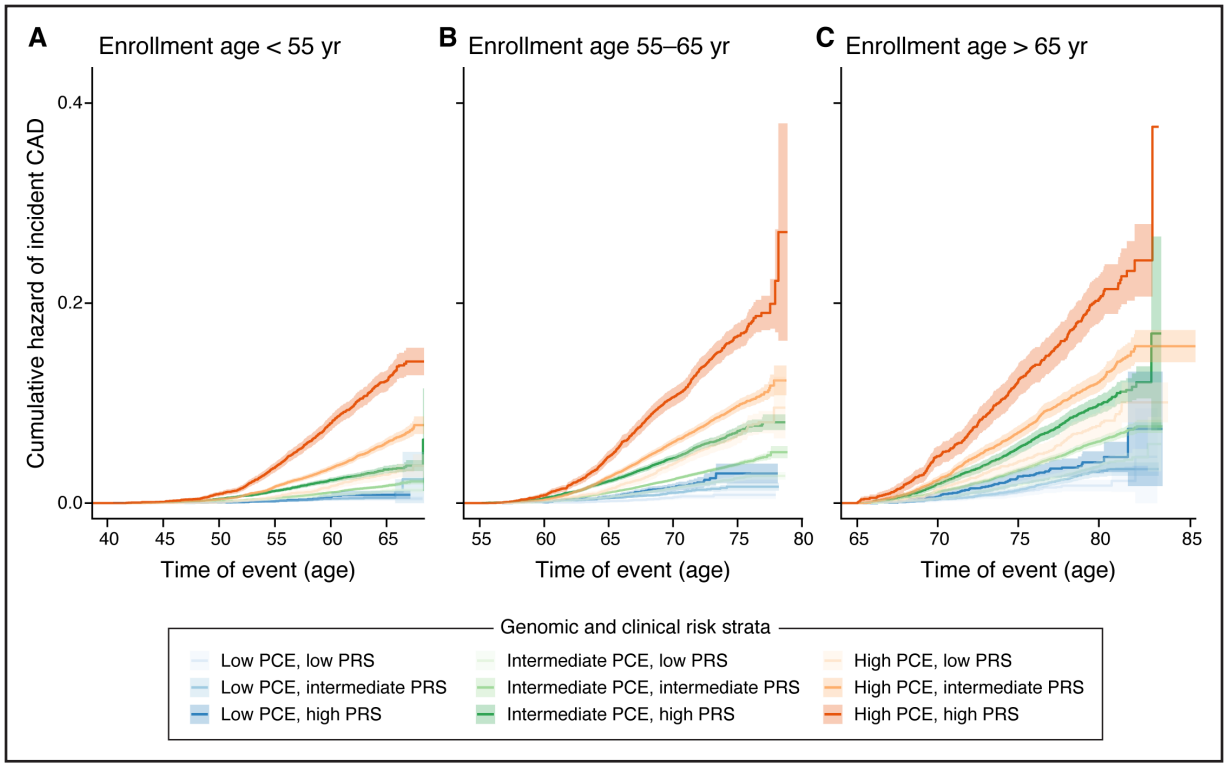

Figure 3. Cumulative hazard of incident coronary artery disease (CAD) by clinical and genomic risk in 3 age groups. In the UK Biobank (N=327 837), 3 age groups (<55, 55–65, and over 65 years) at risk estimation were used to compare the cumulative incidence of CAD by genomic (polygenic risk score [PRS]) and clinical (pooled cohort equations [PCE]) risk levels defined as low (bottom quintile), intermediate (middle 3 quintiles), and high (top quintile) within each age group (see Figure S5; Table S5). We report the cumulative hazard over the observed follow-up time (median, 12.2 years**).** The stratification was highest in the <55 years age group (**A**), where the cumulative hazard ranged from 0.45% (95% CI, 0.23–0.67) for individuals with low PRS and low PCE to 14.6% (95% CI, 12.8–15.5) for individuals with high PRS and high PCE. The stratification decreased but persisted in the older age groups (**B** and **C**). Here, we feature the same *y* axis to emphasize differences in absolute risk among young, middle-aged, and older individuals.

dynamic trajectory.[10] Future approaches need to account for time-varying effects while also considering the time of assessment. This may require the use of time-varying coefficients,[11] multistate models,[12] and a more nuanced approach to handling time-varying competing risks.[13]

Although the relative contribution is much greater, the absolute number of events is lower among this age group within short-to-intermediate time intervals. Thus, there is value in a model that is capable of recognizing high-risk but rare events. Young individuals have higher rates of subsequent events lifelong with potential downstream complications.[14] Furthermore, our analysis highlights interesting sex-specific differences in the FOS cohort. We note the interesting peak of the average HR between the ages 35 to 37 years and the decline after in the FOS population (Figure 1A). In this analysis, we use age as the time scale and report the HR over the follow-up period to ensure consistency in absolute calendar ages among all participants. Participants were considered by their age at first examination to ensure sufficient follow-up and reduce missing data. Most individuals in the FOS cohort had a follow-up period between 27 and 30 years, meaning those under the age of 30 years had minimal overlap with postmenopausal years. In FOS, the median age at enrollment was 36 years, with a median age of 70 years at the end of follow-up. Therefore, younger individuals had peak overlap of menopausal years, making the age of enrollment a proxy for the overall follow-up period, with significant changes observed in those enrolling around age 30 years (Figure S13). In summary, this illustrates the heterogeneity among a cohort that is followed during these important life transitions. Indeed, cardiovascular disease is the leading cause of death in women, particularly increasing postmenopause. Longitudinal studies over the past 20 years have shown that menopause transition contributes to this increased risk due to changes in sex hormones, body composition, lipids, and vascular health.[15–17] These findings highlight the importance of midlife as a critical period for monitoring and early intervention to reduce cardiovascular disease risk. Our results corroborate this transition, as the inflection in the rising HR for younger women is a proxy for those patients who will undergo the menopause transition during the study.[7]

We also demonstrate that CAD PRS allows us to (1) predict lifetime risk earlier in someone's life course and (2) predict events that will occur earlier in life (ie, premature CAD). Although the PCE tends to capture individuals

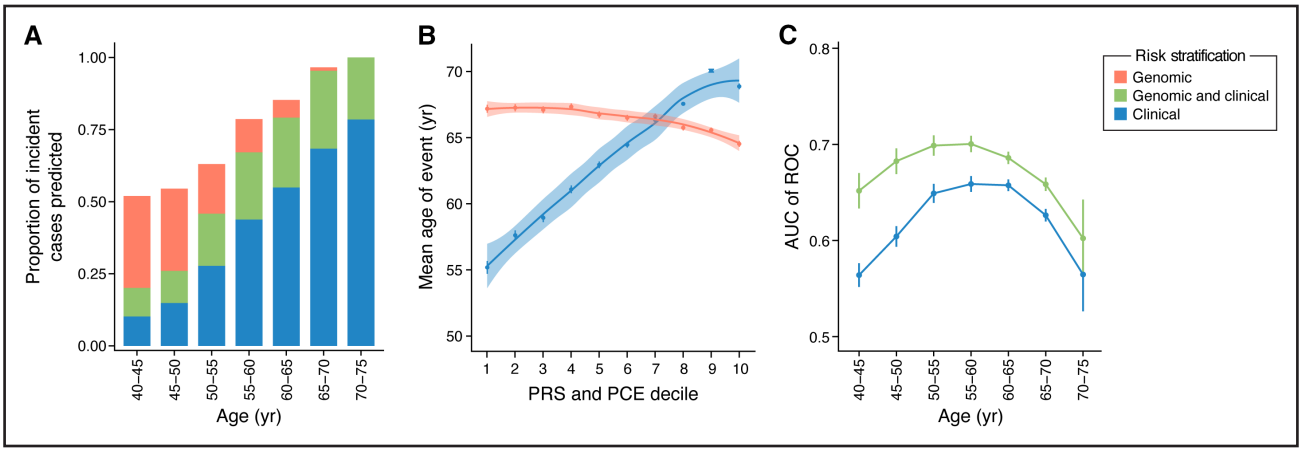

Figure 4. Augmenting risk prediction of coronary artery disease (CAD) in early middle-age with the addition of polygenic risk score (PRS).

A, In the UK Biobank (N=327 837), we show the proportion of cumulative CAD events predicted using high genomic risk (PRS in the top quintile), intermediate to high clinical risk (pooled cohort equations [PCE] 10-year risk ≥7.5%) or both at enrollment, by age of estimation. **B**, Mean age for CAD events decreased with increasing PRS (red), from 67.2 years (95% CI, 66.6–67.8 years) in the lowest decile to 64.5 years (95% CI, 64.1–65.0 years) in the highest decile. Conversely, those in the highest PCE decile (blue) had events 13.7 years later in life than those of the lowest PCE. **C**, Area under the reciever operator curve (AUC) of a model considering only clinical risk, compared with a model combining clinical and genomic risk, for participants between ages 40 and 75 (at the time of risk estimation; in 5- year age strata). Genomic risk categories are defined as: high risk, top quintile of the PRS distribution; intermediate risk, middle 3 quintiles; low risk, bottom quintile. Clinical risk categories are defined by PCE predicted 10-year risk <7.5%, 7.5%–20%, and >20%.

who have higher rates of known clinical risk factors, genetic risk is largely independent with a broadly uniform distribution of clinical risk factors among varying levels of genetic risk. PCE incorporates age as a constant interaction with time-to-risk models but our study shows that this change is not linear nor easily predictable.[3,5]

In conclusion, our work highlights 3 areas in which CAD PRS adds value to current guideline-based clinical risk prediction using the PCE: (1) CAD PRS had the most value in augmenting risk prediction for CAD among individuals younger than 55 years of age. Prior work for CAD has largely examined area under the curve augmentation with PRS in aggregate of middle-aged or even older participants noting minimal incremental value.[18,19] (2) CAD PRS improves precision in risk estimation for individuals within the strata of clinical risk according to the PCE throughout the life course, but such stratification is highest among individuals under the age of 55 years. (3) Integration of genomics in risk prediction enables the detection of premature events that are missed by current guideline-supported tools. Collectively, these findings support inclusion of PRS to augment current clinical risk estimation toward better allocation of preventive therapies.[7,20]

Limitations

Our results should be interpreted in the context of potential limitations. First, survival bias is an important limitation with a broad age of inclusion in any volunteer cohort. However, this also reflects the dynamic importance of risk factors when considering event-free individuals at increasing age, which is leveraged in the present study. Second, the 2 cohorts studied spanned different countries, time periods, and medical guidelines epochs, making absolute estimates between FOS and UKB not directly comparable, but the overall dynamic age-dependent trends were consistent. Third, we do not compare genomic to lifestyle-based 'primordial' risk calculators in individuals under the age of 40 years, which would further illuminate the value of genomics in comparison to those measures before onset of disease risk factors. Fourth, because this study is predominantly of individuals of European ancestry, additional research is needed to evaluate whether these observations are applicable to other ancestries. CAD PRS has reduced performance in ancestries outside of Europe but cross-ethnic transferability of PRS is improving with more diverse training data and novel methods.[21]

Conclusions

In summary, this study extends current CAD risk prediction models by offering a dynamic framework that also includes genomics toward improved prediction. We show that genomic information adds the most information for young and middle-aged individuals when compared with older individuals for the prediction of CAD events.

ARTICLE INFORMATION

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Supplemental Material

Supplemental Methods
Tables S1–S2
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