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ORIGINAL RESEARCH

GENETICS, OMICS, AND TISSUE REGENERATION

Polygenic Risk, Rare Variants, and Family History

Independent and Additive Effects on Coronary Heart Disease

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ABSTRACT

BACKGROUND Genetic factors are not included in prediction models for coronary heart disease (CHD).

OBJECTIVES The authors assessed the predictive utility of a polygenic risk score (PRS) for CHD (defined as myocardial infarction, coronary revascularization, or cardiovascular death) and whether the risks due to monogenic familial hypercholesterolemia (FH) and family history (FamHx) are independent of and additive to the PRS.

METHODS In UK-biobank participants, PRS_{CHD} was calculated using metaGRS, and 10-year risk for incident CHD was estimated using the pooled cohort equations (PCE). The area under the curve (AUC) of the receiver operator curve and net reclassification improvement (NRI) were assessed. FH was defined as the presence of a pathogenic or likely pathogenic variant in *LDLR*, *APOB*, or *PCSK9*. FamHx was defined as a diagnosis of CHD in first-degree relatives. Independent and additive effects of PRS_{CHD}, FH, and FamHx were evaluated in stratified analyses.

RESULTS In 323,373 participants with genotype data, the addition of PRS_{CHD} to PCE increased the AUC from 0.759 (95% CI: 0.755-0.763) to 0.773 (95% CI: 0.769-0.777). The AUC and NRI_{Event} for PRS_{CHD} were higher before the age of 55 years. Of 199,997 participants with exome sequence data, 10,000 had a $PRS_{CHD} \geq$95th percentile (PRS_{P95}), 673 had FH, and 46,163 had FamHx. The CHD risk associated with PRS_{P95} was independent of FH and FamHx. The risks associated with combinations of PRS_{CHD}, FH, and FamHx were additive and comprehensive estimates could be obtained by multiplying the risk from each genetic factor.

CONCLUSIONS Incorporating PRS_{CHD} into the PCE improves risk prediction for CHD, especially at younger ages. The associations of PRS_{CHD}, FH, and FamHx with CHD were independent and additive. (JACC Adv 2023;2:100567)

The cornerstone for primary prevention of coronary heart disease (CHD) is estimating risk using demographic and clinical risk factors and targeting therapy to those most likely to benefit.[1,2] The American College of Cardiology and the American Heart Association guideline on the primary prevention of cardiovascular disease recommends estimating the 10-year risk of CHD using the

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ABBREVIATIONS AND ACRONYMS

AUC = area under the curve

CHD = coronary heart disease

FamHx = family history of CHD

FH = familial hypercholesterolemia

IRS = integrated risk score

LDL-C = low-density lipoprotein cholesterol

NRI = net reclassification improvement

P/LP = pathogenic/likely pathogenic

PCE = pooled cohort equation

PRS = polygenic risk score

UKBB = UK-biobank

pooled cohort equations (PCE).[1,2] Additional risk-enhancing factors, can be considered, especially in those at borderline (10-year risk: 5% to <7.5%) or intermediate (10-year risk ≥7.5% to <20%) risk.[1] Genetic susceptibility factors are not included in the PCE; these include a polygenic risk score (PRS) that represents the additive effect of multiple common variants,[3] rare pathogenic/likely pathogenic (P/LP) variants in *LDLR*, *APOB*, or *PCSK9* with relatively large effects (ie, familial hypercholesterolemia [FH]),[4-6] and positive family history of CHD, which reflects shared genetic and environmental risk factors among relatives.[7]

A PRS for CHD can modify the risk associated with clinical risk factors[8] and the net reclassification improvement (NRI) after incorporating PRS for CHD into existing risk prediction frameworks has ranged from 0.1% to 6% in different cohorts.[9-12] In a randomized clinical trial, disclosure of the PRS resulted in lower low-density lipoprotein cholesterol (LDL-C) levels compared to the disclosure of a conventional risk score alone.[13,14] Patients with monogenic FH are at significantly increased risk of CHD, even after adjustment for LDL-C levels[15] and prospective studies have demonstrated positive family history to be associated with 1.5- to 2.0-fold higher CHD risk, independent of conventional risk factors.[16-18] However, how to combine these 3 genetic susceptibility factors to obtain comprehensive CHD risk profiles is unclear. Therefore, using the UK-Biobank (UKBB) data, we investigated possible independent and additive effects of a PRS, monogenic FH and a positive family history, on CHD risk.

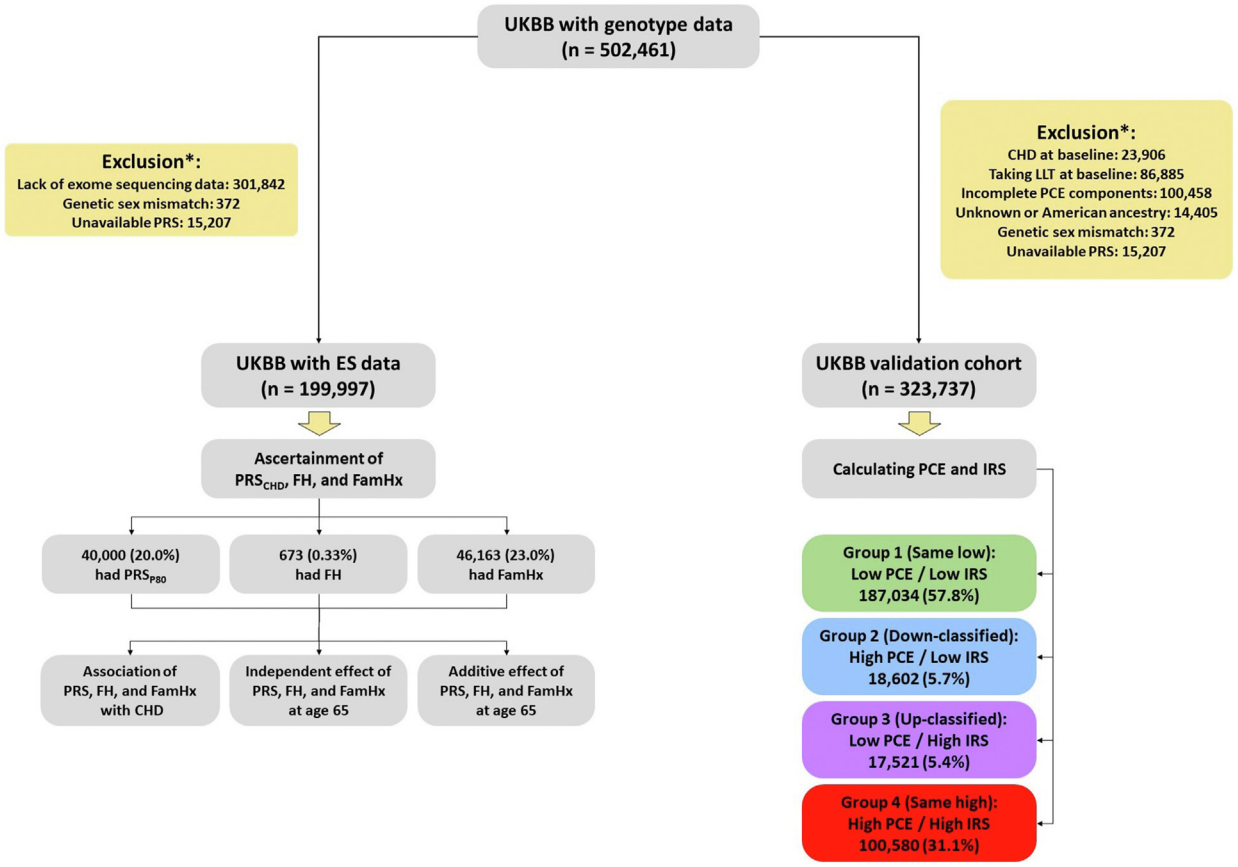
METHODS

UKBB STUDY. The UKBB study design and population have been described in detail elsewhere.[19] Briefly, more than 500,000 participants aged 40 to 70 were recruited between 2006 and 2010 from the general population through 22 assessment centers throughout the United Kingdom. Through extensive questionnaires, interviews, and physical measurements, participants provided information on their past medical history, lifestyle, and other potentially health-related factors (Supplemental Table 1, Supplemental Method 1). Blood samples were collected for biochemical laboratory measurements, genotyping, and exome sequencing. All participants provided written informed consent for the study, and the UKBB study was approved by the Northwest multicenter research ethics committee.[20] We selected participants with genotyping and exome sequence data available and excluded those with a mismatch between reported sex and the genetically inferred sex. The present study was conducted under UKBB application number 79990.

PRS FOR CHD. We used a previously published PRS, metaGRS (PGS catalog number: PGS000018),[21] hereafter denoted as PRS_{CHD}, to estimate the polygenic risk of CHD. The PRS is based on 1.7 million single nucleotide variants (SNVs) and derived from a meta-analytic approach that combines 3 previously developed PRSs.[21] The effect-size estimates for the SNVs used in PRS_{CHD} were obtained, and the PRSice pipeline was used to calculate PRS_{CHD} as a weighted sum based on allele dosages and SNV effect sizes.[22] All scores were standardized to zero-mean and unit variance within each ancestry. To estimate the fraction of different ancestries for each participant, we used the software ADMIXTURE[23] with the 1000 Genome dataset as reference (European, African, Amerindian, East Asian, South Asian) and categorized participants according to their largest estimated admixture fraction (Supplemental Figure 1).[24] We classified individuals into 3 groups, based on their PRS percentiles: ≤20th percentile (PRS_{P20}), percentile 20th to 80th (PRS_{P20-80}), and ≥80th percentile (PRS_{P80}) (Supplemental Method 5). We additionally divided participants in PRS_{P80} into 2 groups, PRS_{P80-95} and PRS_{P95}. The primary outcome was CHD, defined as myocardial infarction, coronary revascularization, or cardiovascular death (Supplemental Table 2). Calibration of the PRS model was assessed graphically by plotting the observed CHD events vs predicted CHD events (Supplemental Figure 2).

CLINICAL RISK SCORE AND INTEGRATED RISK SCORE. From the entire UKBB dataset, we identified individuals without a history of CHD and who were not on lipid-lowering medication at the time of recruitment. We excluded participants with missing genetic data or missing data for the components of PCE and calculated 10-year CHD risk based on PCE (**Figure 1**). We then calculated an ancestry specific standardized PRS_{CHD} as described earlier and estimated an "integrated risk score" (IRS) that incorporates PRS_{CHD} and PCE (details presented in Supplemental Method 2). We defined the "threshold of actionability" as 10-year CHD risk of 7.5% as per the American College of Cardiology/American Heart Association guideline on the primary prevention of atherosclerotic cardiovascular disease.[1] Based on having either high- or low-PCE and IRS, participants were divided into 4 groups (**Figure 1**) and followed for

FIGURE 1 **UKBB Cohort Analyzed for This Study**



Creating a UKBB validation cohort to compare the IRS vs PCE **(right arm)**, and a UKBB cohort with exome sequencing data to asses the effect of genetic factors on CHD, along with their independent, and additive effects on CHD **(left arm)**. *The numbers for each exclusion item may overlap. CHD = coronary heart disease; ES = exome sequencing; FamHx = family history of CHD; FH = familial hypercholesterolemia; IRS = integrated risk score; LLT = lipid lowering treatment; PCE = pooled cohort equation; PRS$_{P\#}$ = percentile of PRS; UKBB = UK-biobank.

incident CHD events. We compared the risk of CHD in those who were up-classified (low-PCE and high-IRS) vs those who were down-classified (high-PCE and low-IRS). Unadjusted Kaplan-Meier curves were used to depict time to event in these groups. To compare IRS vs PCE, we used the area under the curve (AUC) of the receiver operating characteristic curve, net reclassification improvement (NRI) for events (NRI$_{Event}$) and nonevents (NRI$_{Nonevent}$), and integrated discrimination improvement (Supplemental Method 3). To assess how different thresholds of actionability affected our findings, we reran the analyses across 10-year risk of 5% to 40%. Additionally, we assessed performance of IRS in predicting 10-year of CHD risk in different age categories.

MONOGENIC FH AND FAMILY HISTORY OF CHD. To ascertain FH and FamHx, we used the 200k UKBB exome sequence dataset (Figure 1); the details of the sequencing process and quality measures are described elsewhere.[25,26] The CRAM files underwent original quality functional equivalence protocol before calling with Deep-Variant to generate genomic variant call formats,[25] which were aggregated and joint genotyped with GLnexus to create a single multisample VCF for all UKBB 200k samples. We used Variant Effect Predictor (version 104.3)[27] to annotate variants in *LDLR*, *APOB*, and *PCSK9* against the GRCh38.p13 reference genome and added additional information using dbNSFP (dbNSFP4.1a)[28,29] and gnomAD (r2.1.1).[30] Participants with a *LDLR*, *APOB*, or *PCSK9* variant labeled in ClinVar as P/LP for FH were considered to have FH.[15,31,32] *LDLR* variants that were not labeled or had conflicting interpretations of pathogenicity in ClinVar, were considered pathogenic

if they had an allele frequency of <0.0002 and were predicted (*LDLR*, ENST00000558518.6) to be a stop gain, frameshift, in-frame deletion/insertion, or affecting splice acceptor/donor sites by Variant Effect Predictor. Missense variants were considered as P/LP if frequency was <0.0002 and REVEL score >0.75 or affecting a cysteine residue in *LDLR*. Population allele frequency, in silico prediction data, and missense variant criteria were used for variant curation according to the ClinGen guideline (Supplemental Figure 3).[24] FamHx of CHD in a first-degree relative was ascertained using interview data at the time of recruitment (Supplemental Table 1).

ASSOCIATION OF PRS_{CHD}, FH, AND FamHx WITH CHD ACROSS AGE. Using logistic regression models that adjusted for sex and the first 4 principal components of ancestry, we estimated CHD risk associated with PRS_{CHD}, FH, and FamHx in different age groups based on participant age at the last follow-up or CHD event. For this, we used UKBB participants with exome sequence data (**Figure 1**). First, we assessed the association of genetic factors with CHD in 4 age groups: <50, 50 to 60, 60 to 70, and >70 years. Next, we assessed the association of genetic factors with CHD across the age spectrum, by categorizing participants into groups of 5 years: 45 to 50, 50 to 55, 55 to 60, 60 to 65, 65 to 70, 70 to 75, and >75 years. Participants were considered "case" if they had CHD at the given age group, and "control" when either age at CHD diagnosis was after the age group or they did not have any CHD events. Participants who did not reach to that age or had CHD before the given age group were not included in the analysis.

INDEPENDENT AND ADDITIVE EFFECT OF PRS_{CHD}, FH, AND FamHx. In UKBB participants with exome sequence data, we assessed the independent and additive effect of PRS_{CHD} on FH and FamHx on CHD at 65 years which was equal to the median age plus median follow-up duration of the cohort (**Figure 1**). In a stratified analysis, participants were divided into subgroups based on whether they had any of the 3 genetic risk factors. The CHD risk associated with the other 2 factors was studied using logistic regression models as described above.

In logistic regression analyses, we assessed for interactions of PRS_{CHD} with FH or FamHx and assessed the CHD risk associated with combinations of PRS_{CHD} with FH and FamHx. To evaluate the additive effect of FH and FamHx, individuals without FH and without FamHx of CHD ($FH^{-}FamHx^{-}$) were considered as the reference group. To evaluate the additive effect of PRS_{CHD} and FH, we categorized individuals into 6 categories (PRS_{P20}, $PRS_{P20\text{-}80}$, and PRS_{P80} combined with FH and FH^{-}), with $PRS_{P20\text{-}80}FH^{-}$ as the reference group. To assess the additive effect of PRS_{CHD} and FamHx, we binned participants into 4 groups (PRS_{P20}, $PRS_{P20\text{-}80}$, $PRS_{P80\text{-}95}$, and PRS_{P95}) and then included family history status to create 8 groups, considering $PRS_{P20\text{-}80}FamHx^{-}$ as the reference group. Unadjusted Kaplan-Meier curves were drawn to depict time to event in these groups, and using generalized linear models, we assessed whether these 3 factors affect CHD risk independently and additively (Supplemental Method 4).

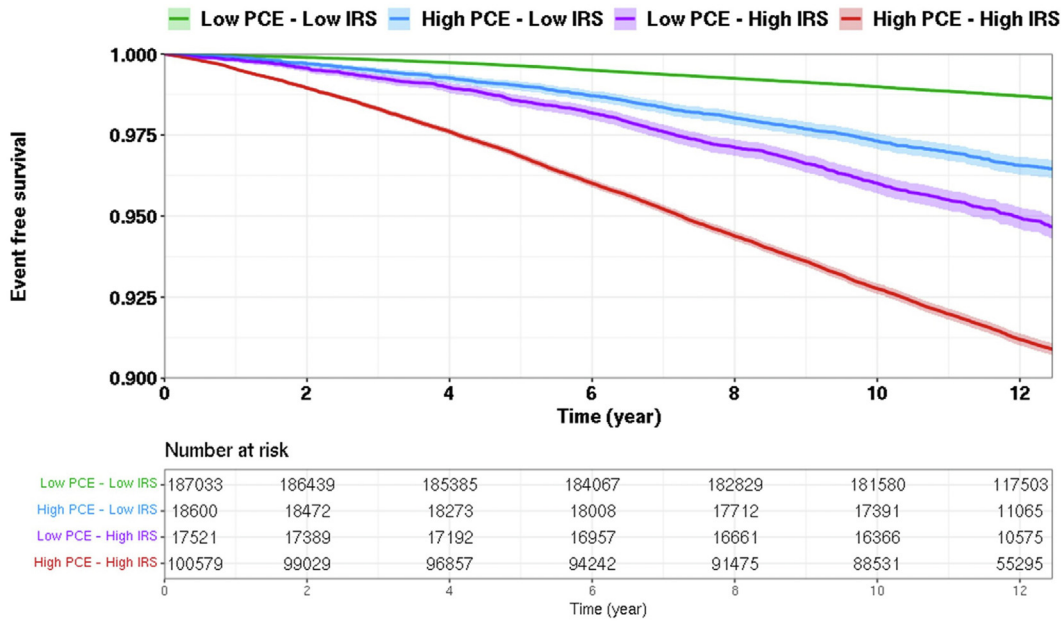
Statistical analyses were performed using R (version 3.6.3, R Foundation for Statistical Computing). All tests were 2-sided, and *P* values <0.05 were considered statistically significant.

RESULTS

CHD RISK ASSOCIATED WITH PRS_{CHD}. Of the 502,461 genotyped UKBB participants, we excluded 302,464 because of discrepancies between self-reported and genetically ascertained sex, lack of exome sequence data, and no available PRS_{CHD} data (**Figure 1**). Of the remaining 199,997; 10,000 had PRS_{P95}. The characteristics of the participants are presented in Supplemental Table 3. The CHD risk associated with PRS_{CHD} at different age categories is summarized in Supplemental Table 4. Before age 50 years, the OR for CHD for $PRS_{P80\text{-}95}$ was 1.73 (95% CI: 1.50-2.00, $P < 0.001$) and for PRS_{P95} was 3.25 (95% CI: 2.73-3.85, $P < 0.001$), while in participants aged >70 years, the OR for $PRS_{P80\text{-}95}$ decreased to 1.33 (95% CI: 1.22-1.46, $P = 0.010$) as well OR for PRS_{P95}: 1.91 (95% CI: 1.68-2.17, $P < 0.001$).

RECLASSIFICATION AFTER INCORPORATING PRS INTO PCE. Of 502,461 participants in UKBB, 178,724 were excluded (reasons for exclusion are outlined in **Figure 1**), leaving 323,737 for assessment of IRS vs PCE. The characteristics of the participants are summarized in Supplemental Table 3 and the distribution of PCE and IRS in the population is depicted in Supplemental Figure 4. Considering 7.5% as the threshold for actionability, 287,614 (88.9%) participants had concordant risk assignment based on PCE and IRS (same low or same high), whereas 36,123 (11.1%) were reclassified. Of these, 18,602 (5.7%) participants had high-PCE and low-IRS (down-classified), and 17,521 (5.4%) had low-PCE and high-IRS (up-classified) (**Figure 1**). Comparing the 2 groups, the up-classified group was younger (age 56.94 ± 6.62 years vs 60.78 ± 5.81 years, $P < 0.001$) and more often female (60.4% vs 43.8%, $P < 0.001$) (Supplemental Table 5). The distribution of predicted 10-year PCE, PRS, and IRS in these 2 groups is depicted in

FIGURE 2 Kaplan-Meier Curves for Survival Free of CHD Events



The numbers of at-risk in each group are displayed. The **green line** represents low PCE/low IRS, the **blue line** represents high PCE/low IRS, the **purple line** represents low PCE/high IRS, and the **red line** represents high PCE/high IRS. Abbreviations as in Figure 1.

Supplemental Figure 5. The reclassification rate varied based on age, gender, and ancestry (Supplemental Figure 6). During a follow-up of 12.11 ± 1.62 years, 12,828 (3.96%) participants developed CHD. Kaplan-Meier curves for CHD-free survival in the 4 groups are shown in **Figure 2**.

The up-classified group was at an increased risk of myocardial infarction, HR: 1.80 (95% CI: 1.50-2.17), and coronary revascularization, HR: 2.40 (95% CI: 2.08-2.77), and CHD, HR: 1.48 (95% CI: 1.34-1.64), compared to the down-classified group (**Table 1**). At the actionable threshold of 7.5% 10-year risk, the risk of CHD for up-classification was higher at younger age compared to older ages (Supplemental Figure 7).

Model AUC for CHD was 0.759 (95% CI: 0.755-0.763) for PCE, improving to 0.773 (95% CI: 0.769-0.777) for the IRS (*P* diff <0.001). The IRS had greater predictive power in participants aged <55 years (AUC: 0.796 [95% CI: 0.788-0.804]) than in those aged ≥55 years (AUC: 0.724 [95% CI: 0.719-0.729]) (*P* diff <0.001). Further, the IRS had greater predictive power in participants at lower risk based on PCE than in higher risk participants (AUC for <7.5% baseline PCE risk was 0.729 [95% CI: 0.721-0.737], while AUC for ≥7.5% baseline PCE risk was 0.653 [95% CI: 0.647-0.658)] *P* diff <0.001) (Supplemental Figure 8).

The percentage of reclassified participants, corresponding NRI_{Event}, $NRI_{Nonevent}$, and the HR of CHD in up-classified group vs down-classified group across different actionable thresholds are depicted in Supplemental Figures 9 and 10. Considering 10-year risk of 7.5% as the actionable threshold, the IRS resulted in an NRI_{Event} of 2.77% for myocardial infarction, 4.72% for coronary revascularization, and 1.96% for CHD (Supplemental Table 6). The NRI_{Event} for CHD in participants <55 years of age was 10.94% (9.71%-12.53%) while for those ≥55 years of age it was −0.55% (−1.10% to 0.07%).

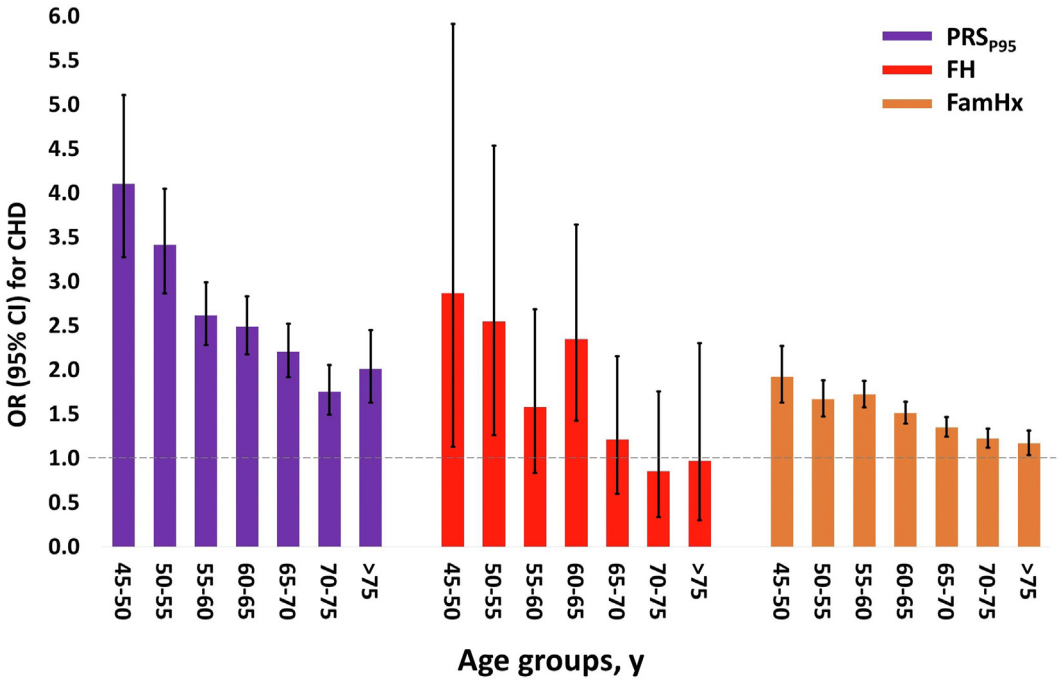
RISK ASSOCIATED WITH FH AND FamHx. 673 (0.33%, ~1:300) had FH, and 46,163 (23.0%) had FamHx of

TABLE 1 CHD Risk of Participants Who Were Reclassified After Incorporation of PRS_{CHD}

	High PCE/Low IRS (Down-Classified) (n = 18,602)	Low PCE/High IRS (Up-Classified) (n = 17,521)	HR (95% CI)	*P* Value
Myocardial infarction	178 (1.0)	303 (1.7)	1.80 (1.50-2.17)	<0.001
Coronary revascularization	266 (1.4)	602 (3.4)	2.40 (2.08-2.77)	<0.001
Cardiovascular death	310 (1.7)	232 (1.3)	0.79 (0.66-0.93)	<0.001
CHD	641 (3.4)	893 (5.1)	1.48 (1.34-1.64)	<0.001

Values are n (%) unless otherwise indicated.
CHD = coronary heart disease; IRS = integrated risk score; PCE = pooled cohort equation.

FIGURE 3 The Association of Genetic Factors With CHD Across Age



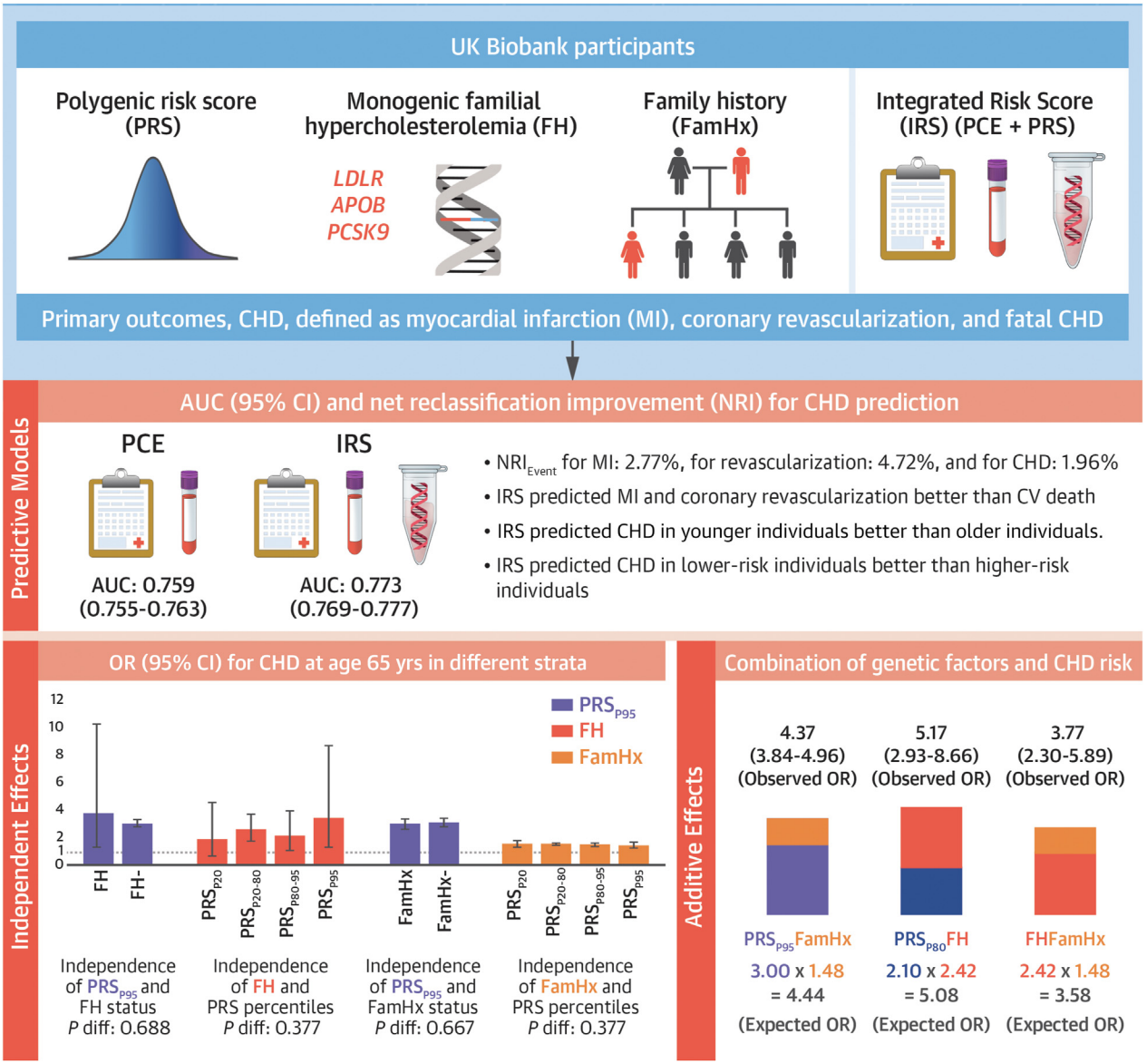
Using a regression model adjusted for sex and the first 4 principal components of ancestry, we estimated the ORs (95% CI) for CHD associated with PRS_{P95}, monogenic FH, and FamHx in different age categories. Abbreviations as in **Figure 1**.

CHD. The CHD risk associated with FH and FamHx at different age categories is summarized in Supplemental Table 4, and **Figure 3**. Before age 50, the OR for CHD for FH and FamHx was 2.79 (95% CI: 1.43-4.85, $P = 0.001$) and 1.65 (95% CI: 1.46-1.86, $P < 0.001$), respectively. In participants >70 years, the OR for FH, and FamHx declined to 0.94 (95% CI: 0.48-1.66, $P = 0.845$) and 1.20 (95% CI: 1.11-1.28, $P = 0.010$), respectively.

INDEPENDENT EFFECT OF PRS_{CHD}, FH, AND FamHx. At age 65 years, the OR for CHD associated with PRS_{P95} was similar in FH and FH^- [3.79 (95% CI: 1.29-10.37) vs 3.06 (95% CI: 2.83-3.32), P diff = 0.688], and also similar in FamHx and FamHx− [2.93 (95% CI: 2.56-3.35) vs 3.04 (95% CI: 2.75-3.36), P diff = 0.667]. FamHx was associated with a similar increase in the risk of CHD across the spectrum of PRS_{CHD}: [1.51 (95% CI: 1.28-1.77) in PRS_{P20}, 1.51 (95% CI: 1.41-1.62) in $PRS_{P20\text{-}80}$, 1.45 (95% CI: 1.31-1.62) in $PRS_{P80\text{-}95}$, and 1.42 (95% CI: 1.22-1.65) in PRS_{P95}, P diff = 0.450). A similar pattern of increased CHD risk was observed for the risk associated with FH across the PRS_{CHD} and family history status (Supplemental Table 7, Supplemental Figure 11, **Central Illustration**). The results of the sex-stratified analysis revealed that the effects of the 3 genetic susceptibility factors were similar and independent in both men and women (Supplemental Tables 8 and 9).

ADDITIVE EFFECT OF PRS_{CHD}, FH, AND FamHx. The additive risk of CHD due to combinations of PRS_{CHD}, FH, and FamHx is illustrated in **Figure 4** and the **Central Illustration**. At age 65 years, considering those without monogenic FH and who were in the 3 middle quintiles for PRS_{CHD} ($PRS_{P20\text{-}80}$ FH^-) as the reference group, the ORs for CHD in $PRS_{P20\text{-}80}$ FH was 2.68 (95% CI: 1.77-3.90, $P < 0.001$), in $PRS_{P80}FH^-$ was 2.13 (95% CI: 2.02-2.25, $P < 0.001$) and in PRS_{P80}FH was 5.17 (95% CI: 2.93-8.66, $P < 0.001$). In comparison to the group with no FamHx and the 3 middle quantiles for PRS_{CHD} ($PRS_{P20\text{-}80}$FamHx−) the OR for CHD in $PRS_{P80\text{-}95}$FamHx was 2.68 (95% CI: 2.44-2.94, $P < 0.001$) and in PRS_{P95}FamHx was 4.37 (95% CI: 3.84-4.96, $P < 0.001$). (**Figure 4**, Supplemental Figures 12 to 14). In analyses conducted separately in men and women, results were similar, demonstrating that the effects of the 3 genetic susceptibility factors were additive in both sexes (Supplemental Figures 15 and 16).

CENTRAL ILLUSTRATION **The Incremental Predictive Utility of PRS_{CHD}, as Well as the Independent and Additive Effects of Genetic Factors for the Risk of CHD**



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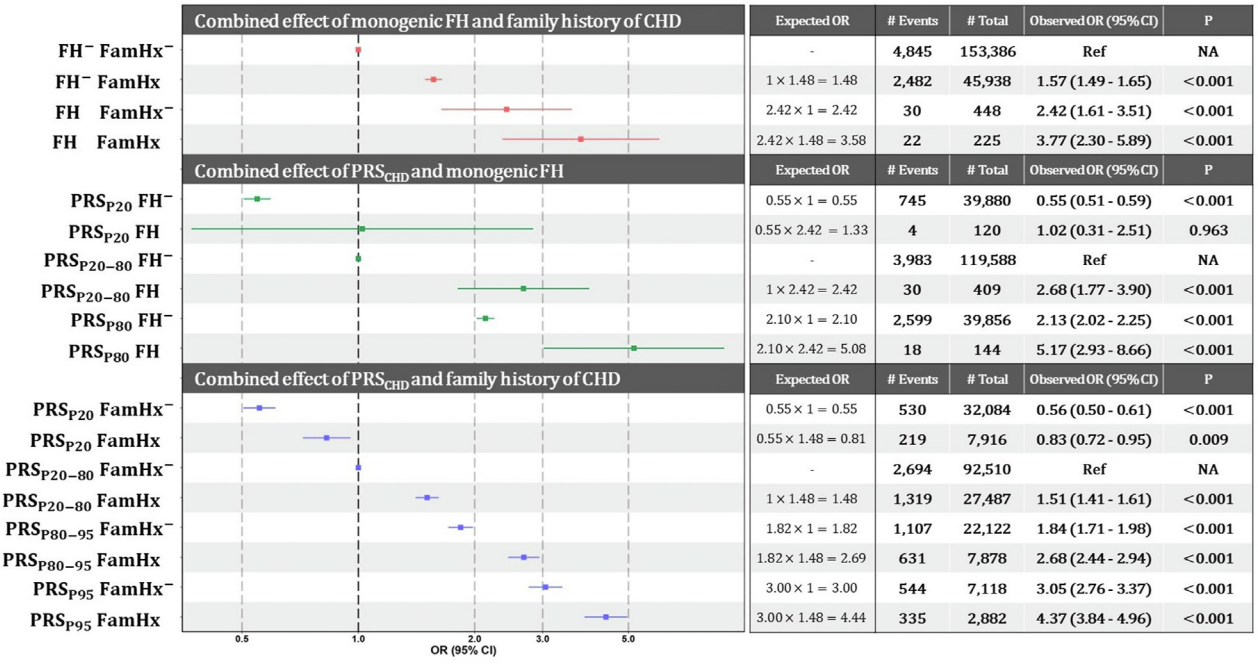
(Top panel) The UKBB data set was used to calculate the PRS, identify FH variants, and ascertain FamHx of CHD. By combining PCE and PRS, an IRS was developed to predict the incidence of the primary outcome, CHD. **(Middle panel)** The IRS outperformed the PCE in predicting the incidence of CHD, particularly in younger and lower-risk individuals. **(Bottom panel, left)** Three genetic susceptibility factors independently increased the risk of CHD, with each factor exerting its effect on CHD risk regardless of the presence or absence of the other genetic risk factors. **(Bottom panel, right)** The effect of 3 genetic susceptibility factors was also found to be additive. When more than one genetic factor was present, the risk of CHD could be estimated by multiplying the individual risks contributed by each genetic factor. *APOB* = apolipoprotein B; AUC = area under curve; CHD = coronary heart disease; CV = cardiovascular; FamHx = family history of CHD; FH = familial hypercholesterolemia; IRS = integrated risk score; *LDLR* = low density lipoprotein receptor gene; MI = myocardial infarction; NRI = net reclassification improvement; *P* diff = *P* value for difference; PCE = pooled cohort equations; *PCS9* = proprotein convertase subtilisin/kexin type 9 gene; PRS = polygenic risk score; $PRS_{P\#}$ = percentile of PRS; UK = United Kingdom.

FIGURE 4 Additive Effect of PRS_{CHD}, FH, and FamHx on CHD



Expected OR	# Events	# Total	Observed OR (95% CI)	P
-	4,845	153,386	Ref	NA
1 × 1.48 = 1.48	2,482	45,938	1.57 (1.49 - 1.65)	<0.001
2.42 × 1 = 2.42	30	448	2.42 (1.61 - 3.51)	<0.001
2.42 × 1.48 = 3.58	22	225	3.77 (2.30 - 5.89)	<0.001
Expected OR	**# Events**	**# Total**	**Observed OR (95% CI)**	**P**
0.55 × 1 = 0.55	745	39,880	0.55 (0.51 - 0.59)	<0.001
0.55 × 2.42 = 1.33	4	120	1.02 (0.31 - 2.51)	0.963
-	3,983	119,588	Ref	NA
1 × 2.42 = 2.42	30	409	2.68 (1.77 - 3.90)	<0.001
2.10 × 1 = 2.10	2,599	39,856	2.13 (2.02 - 2.25)	<0.001
2.10 × 2.42 = 5.08	18	144	5.17 (2.93 - 8.66)	<0.001
Expected OR	**# Events**	**# Total**	**Observed OR (95% CI)**	**P**
0.55 × 1 = 0.55	530	32,084	0.56 (0.50 - 0.61)	<0.001
0.55 × 1.48 = 0.81	219	7,916	0.83 (0.72 - 0.95)	0.009
-	2,694	92,510	Ref	NA
1 × 1.48 = 1.48	1,319	27,487	1.51 (1.41 - 1.61)	<0.001
1.82 × 1 = 1.82	1,107	22,122	1.84 (1.71 - 1.98)	<0.001
1.82 × 1.48 = 2.69	631	7,878	2.68 (2.44 - 2.94)	<0.001
3.00 × 1 = 3.00	544	7,118	3.05 (2.76 - 3.37)	<0.001
3.00 × 1.48 = 4.44	335	2,882	4.37 (3.84 - 4.96)	<0.001

The observed ORs (95% CI) for CHD associated with different combinations of PRS_{CHD}, FH, and FamHx at age 65 years were estimated using logistic regression models adjusted for sex and the first 4 principal components of ancestry. The expected ORs were estimated by multiplying the crude independent risk, based on Supplemental Table 10. The $FH^{-}FamHx^{-}$ group was considered as the reference for studying the additive effect of FH and FamHx (*P* interaction between FH and FamHx: 0.986) **(top panel)**. $PRS_{P20-80}FH^{-}$ was considered as the reference group for studying the additive effect of PRS_{CHD} and FH (*P* interaction between PRS_{P20} and FH: 0.522, *P* interaction between PRS_{P80} and FH: 0.771) **(middle panel)**. $PRS_{P20-80}FamHx^{-}$ was considered as the reference group for studying the additive effect of PRS_{CHD} and FamHx (*P* interaction between PRS_{P20} and FamHx: 0.916, *P* interaction between PRS_{P80-95} and FamHx: 0.607, *P* interaction between PRS_{P95} and FamHx: 0.559) **(lower panel)**. CI = confidence interval; $PRS_{P\#}$ = Percentile of PRS_{CHD}.

DISCUSSION

The main findings of our study were, 1) incorporating a PRS into PCE improved CHD risk prediction and 2) the risks from monogenic familial hypercholesterolemia and family history of CHD were independent of and additive to PRS_{CHD}, and the 3 genetic risk factors could be combined to improve accuracy of risk estimates for CHD. Whereas previous reports have shown that incorporation of PRS into PCE could improve CHD risk prediction, our study extend these results by demonstrating that the IRS is of greater predictive value in younger individuals and lower-risk populations and that the effect of genetic susceptibility factors diminishes with age.

Since PRS_{CHD} was only weakly associated with PCE (beta = 0.0007, 95% CI 0.0002-0.0012, $P < 0.001$) (Supplemental Figure 17), we were able to integrate it into PCE as an independent variable. The IRS had a greater predictive value at younger ages. In younger individuals, where traditional risk factors may not have manifested, using a PRS_{CHD} may be particularly helpful in assessing CHD risk. Compared to PCE, IRS was associated with higher hazard for CHD in younger individuals (<55 years) than in older individuals (Supplemental Figure 7), as well in populations with borderline risk (10-year: 5%-7.5%) and intermediate risk (10-year: 7.5%-20%). These finding highlight the potential utility of a PRS_{CHD} in younger adults and in those considered at low or intermediate risk based on PCE.

Polygenic risk can be measured early in life before conventional risk factors have manifested, and lipid-lowering treatment and lifestyle changes could be implemented to reduce the risk due to a high PRS, similar to what is recommended for patients with FH.[14,33] Our results indicate that nearly the entire spectrum of PRS could be used, not simply dichotomous characterization as high (top 5th percentile) vs not high (<95th percentile). Those in the 80th to 95th

percentile were also at an increased risk of CHD: OR was 1.82 (95% CI: 95% CI: 1.71-1.93, $P < 0.001$), and those with a low PRS (lowest 20th percentile) had a lower risk of CHD compared to the 3 middle quintiles: OR was 0.55 (95% CI: 0.51-0.60, $P < 0.001$). Those with PRS_{CHD} in the top fifth percentile had a similar CHD risk at age 65 as those with monogenic FH, consistent with earlier reports (OR: 3.00 [95% CI: 2.77-3.25] vs OR: 2.43 [95% CI: 1.77-3.26], P diff = 0.191). While the prevalence of monogenic FH was relatively low (0.3%-0.4%), the number of individuals with PRS_{P95} is at least 10 times greater (5% for the top fifth percentile), emphasizing the significantly greater population-attributable CHD risk due to a high PRS.[3]

Our findings are consistent with previous reports of 2 to 3 times higher risk of CHD in those with monogenic FH even after adjustment for LDL-C levels.[15,31] Prospective studies have demonstrated that positive family history is associated with CHD risk independent of conventional risk factors with ORs ranging from 1.5 to 2.0.[34] Recent studies suggest that adding family history to PRS improves risk prediction for prostate, breast, and colorectal cancer.[35-37] We demonstrated that even after adjustment for PRS_{CHD} and monogenic FH, a positive family history increased the risk of CHD by ~50% (OR: 1.48 [95% CI: 1.41-1.56], $P < 0.0001$). This effect was consistent across different PRS strata and even in those with monogenic FH (Supplemental Table 7). By potentially capturing environmental factors, epigenetic factors, as well as gene-environment interactions[38] family history can identify those with increased risk, independent of PRS, or rare pathogenic variants.[7]

The effects of genetic factors attenuated with age and ORs for high PRS_{CHD}, FH, and FamHx were higher in younger individuals compared to older ones (**Figure 3**). Similar attenuation of the effect of high PRS_{CHD} with age was reported in the Framingham Offspring Study and the ARIC (Atherosclerosis Risk In Communities) cohort.[39,40] Additionally, we noted that a pathogenic/likely pathogenic FH variant was not associated with incident CHD risk after the sixth decade. Similarly, a positive family history had a stronger association with CHD in younger individuals.

Our findings suggest that genetic risk factors (PRS, FH, and FamHx) could inform interventions to reduce CHD risk. The PRS_{CHD} percentile had a sigmoid shape relationship with CHD risk with a linear association between percentiles 10th and 90th, and a steeper increase or decrease in those with PRS ≥90th percentile and ≤10th percentile. FH (OR: ~2.5) and FamHx (OR: ~1.5) moved this curve further up (Supplemental Figure 18).[41] As illustrated in the **Central Illustration** and **Figure 4**, CHD risk associated with different combinations of PRS categories, FH, and FamHx status could be estimated by multiplying their corresponding ORs. Thus, PRS_{CHD}, monogenic etiology of FH, and family history could be combined to generate comprehensive CHD risk estimates and improve risk stratification. The concept of comprehensive risk scores is being evaluated in eMERGE Network phase IV where PRS, monogenic variants, and family history are integrated into conventional risk scoring systems for several common diseases, to increase predictive accuracy.[42]

STUDY STRENGTHS AND LIMITATIONS. The availability of genotypes, exome sequences, and family history data in a large cohort with minimal loss to follow-up enabled us to assess independent and additive effect of elevated PRS, FH, and FamHx on CHD risk. Low ancestral/ethnic diversity in the UKBB cohort is a limitation of our study. Although we did not restrict our analyses to European ancestry individuals, other ancestry groups contributed only modestly to the sample size. Further studies are needed in diverse ancestry groups. The PCE were developed and validated in cohorts from United States and may not be fully generalizable to the UK population. Because of the structure of data in UKBB, we could not ascertain the parent's or sibling's age at the time of the event and rather, the number of affected subjects in the family, so we treated family history of CHD as a dichotomous variable. More granular data may provide incremental information. We used a computational approach to ascertain FH-associated variants since manual curation of variants by a specialist was not feasible.[41]

CONCLUSIONS

Incorporation of a PRS_{CHD} into an existing clinical risk scoring system increased the predictive power for CHD, especially in younger adults. The CHD risk due to monogenic familial hypercholesterolemia and family history was independent of and additive to PRS_{CHD}. Our findings suggest that PRS, monogenic familial hypercholesterolemia, and family history can be incorporated into existing risk prediction frameworks to compute comprehensive risk scores for CHD. This concept has important implications for use of genetic factors in the clinical setting to refine risk stratification for CHD.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Incorporating a PRS into the PCE improves CHD risk prediction, particularly in younger individuals and lower-risk individuals (10-year risk <20%).

TRANSLATIONAL OUTLOOK: Since the effect of PRS, FH, and family history are independent and additive, these can be used together to obtain a comprehensive assessment of CHD risk.

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KEY WORDS **cardiovascular diseases, coronary disease, genetic predisposition to disease, genome-wide association study, risk assessment**

APPENDIX **For supplemental methods, tables, and figures, please see the online version of this paper.**