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ORIGINAL ARTICLE

Heterogeneity of the Predictive Polygenic Risk Scores for Coronary Heart Disease Age-at-Onset in Three Different Coronary Heart Disease Family-Based Ascertainments

Mary F. Feitosa, PhD; Allison L. Kuipers, PhD; Mary K. Wojczynski, PhD; Lihua Wang, PhD; Emma Barinas-Mitchell, PhD; Alexander M. Kulminski, PhD; Bharat Thyagarajan, MD, PhD; Joseph H. Lee, DrPH; Thomas Perls, MD, MPH; Kaare Christensen, DMSc; Anne B. Newman, MD, MPH; Joseph M. Zmuda, PhD; Michael A. Province, PhD

BACKGROUND: Polygenic risk scores (PRS) for coronary heart disease (CHD) may contribute to assess the overall risk of CHD. We evaluated how PRS may influence CHD risk when the distribution of age-at-onset, sex, and family health history differ significantly.

METHODS: Our study included 3 family-based ascertainments: LLFS (Long Life Family Study, $N_{Individuals}$=4572), which represents a low CHD risk, and Family Heart Study, which consists of randomly selected families (FamHS-random, $N_{Individuals}$=1806), and high CHD risk families (FamHS-high risk, $N_{Individuals}$=2301). We examined the effects of PRS, sex, family ascertainment, PRS interaction with sex (PRS*sex) and with family ascertainment (PRS*LLFS and PRS*FamHS-high risk) on CHD, corrected for traditional cardiovascular risk factors using Cox proportional hazard regression models.

RESULTS: Healthy-aging LLFS presented ≈17 years delayed for CHD age-at-onset compared with FamHS-high risk ($P<1.0\times10^{-4}$). Sex-specific association ($P<1.0\times10^{-17}$) and PRS*sex ($P=2.7\times10^{-3}$) predicted prevalent CHD. CHD age-at-onset was associated with PRS (hazard ratio [HR], 1.57; $P=1.3\times10^{-5}$), LLFS (HR, 0.54; $P=2.6\times10^{-5}$), and FamHS-high risk (HR, 2.86; $P=6.70\times10^{-15}$) in men, and with PRS (HR, 1.76; $P=7.70\times10^{-3}$), FamHS-high risk (HR, 4.88; $P=8.70\times10^{-10}$), and PRS×FamHS-high risk (HR, 0.61; $P=3.60\times10^{-2}$) in women. In the PRS extreme quartile distributions, CHD age-at-onset was associated ($P<0.05$) with PRS, FamHS-high risk, and PRS interactions with both low and high CHD risk families for women. For men, the PRS quartile results remained similar to the whole distribution.

CONCLUSIONS: Differences in CHD family-based ascertainments show evidence of PRS interacting with sex to predict CHD risk. In women, CHD age-at-onset was associated with PRS, CHD family history, and interactions of PRS with family history. In men, PRS and CHD family history were the major effects on the CHD age-at-onset. Understanding the heterogeneity of risks associated with CHD end points at both the personal and familial levels may shed light on the underlying genetic effects influencing CHD and lead to more personalized risk prediction.

Key Words: aging ■ cardiovascular diseases ■ coronary artery disease ■ risk factors

Coronary heart disease (CHD) is the number one cause of death in the United States, based on the 2020 report from the American Heart Association,[1] which accounted for ≈13% of the fatalities, causing 365 914 deaths in 2017 and the leading cause of cardiovascular diseases (42.6%). There are substantial sex and age differences in CHD manifestations, where men are more likely to develop a CHD event earlier in life than

Correspondence to: Mary F. Feitosa, PhD, Farrell Learning Center, room 611, 520 S Euclid Ave, Campus Box 8506-98-601, St. Louis, MO 63110. Email mfeitosa@wustl.edu

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Nonstandard Abbreviations and Acronyms

CHD	coronary heart disease
FamHS	Family Heart Study
FamHS-high risk	high CHD risk FamHS families
FamHS-random	randomly selected FamHS families
GWAS	genome-wide association studies
HDL-C	high-density lipoprotein cholesterol
HR	hazard ratio
HR	hazard ratio probability
LDL-C	low-density lipoprotein cholesterol
LLFS	Long Life Family Study
MESA	Multi-Ethnic Study of Atherosclerosis
OR	odds ratio
PRS	polygenic risk scores
SNP	single nucleotide polymorphism

women. In general, men present a macrovascular disease characterized by coronary occlusion and deposition of plaque, while women have a microvascular disease manifesting increased arteriolar constriction and vasospasm.[2] The progressive age-related changes in anatomy and physiology interact with cumulative exposure to traditional cardiovascular risk factors influencing the probability of developing CHD differently in men and women.[3]

Genome-wide association studies (GWAS) have identified over a 150 common genetic variants associated with coronary artery disease.[4–8] Although each variant has a small effect size, the joint effect of associated variants from GWAS summary statistics through polygenic risk scores (PRS) may increase the relative estimation of an individual's overall CHD risk and improve the ability to stratify the population into risk categories. Sex differences in CHD are well known, but sex-specific GWAS and PRS analyses have been sparse to date. Family history also reveals shared genetic and environmental factors, which contribute to predicting CHD.[9–11] However, it remains uncertain how genetic risks, sex, and family history influence the individual's risk of manifesting CHD. To better understand the underlying genetic architecture that predisposes to CHD, it is relevant to investigate CHD outcomes based on differences in sex, age, and family history for CHD, among other cardiovascular risk factors.

The objective of this study is to evaluate whether PRS for CHD could contribute to an individual's risk for CHD age-at-onset accounting for sex differences and CHD family history from 3 different sampling design studies: (1) low CHD risk families from the LLFS (Long Life Family Study), which were enriched for extreme longevity,[12] (2) population average random families from the Family Heart Study (FamHS-random), and (3) high-risk FamHS families enriched for CHD (FamHS-high risk).[13]

METHODS

Data Availability

The research was conducted in 2 family-based studies, LLFS and FamHS. LLFS is an ongoing prospective study designed to determine genetic, behavioral, and environmental factors related to families of exceptionally healthy, elderly individuals. FamHS is half randomly sampled (FamHS-random) and half selected for cardiovascular disease or CHD risk factor abnormalities (FamHS-high risk). Because of the personal nature of LLFS and FamHS, their data are not available online. Requests to access genetic and phenotype data may be submitted via a research plan form to dbGaP (LLFS: phs000397.v1.p1 and FamHS: phs000221.v1.p1). Each participant from LLFS and FamHS provided his/her consent. The Institutional Review Boards approved all study procedures of all participating institutions of LLFS and FamHS.

Full descriptions of the methods are available in the Data Supplement. Figure I in the Data Supplement displays a flowchart of the study. Table I in the Data Supplement shows the GWAS literature and resource data used to create the 176-single nucleotide polymorphism (SNP) PRS.

RESULTS

Description Analyses

Table 1 describes the sample sizes and baseline characteristics from LLFS and FamHS cohorts. Compared with individuals from LLFS, FamHS-high risk participants were ≈20 years younger at baseline and had significantly higher levels of type 2 diabetes, LDL-C (low-density lipoprotein cholesterol), smoking, drinking, and lower HDL-C (high-density lipoprotein cholesterol) levels and hypertension. In LLFS and FamHS cohorts (Table II in the Data Supplement), men had higher CHD prevalence, type 2 diabetes, and hypertension than women, while HDL-C levels were higher in women than men, as expected. LDL-C levels were higher in women for LLFS but lower in both FamHS cohorts than men.

The CHD frequencies were 11.8% in LLFS, 7.8% in FamHS-random, and 18.3% in FamHS-high risk (Table III in the Data Supplement). In LLFS, the mean age on the last contact was 76.5 years in individuals without CHD and ≈4 years earlier in individuals with CHD (Figure II in the Data Supplement). The mean age (≈55) was similar between individuals with and without CHD in total FamHS (Figure III in the Data Supplement). Compared with both FamHS cohorts in the PRS >75% group, LLFS showed a delayed age-at-onset for CHD of ≈17 years (Table III in the Data Supplement).

The allele frequencies for the 176 SNPs in PRS did not differ among LLFS, FamHS-high risk, and FamHS-random. The descriptive analyses and distributions of

Table 1. Baseline Characteristics of Variables by Family Ascertainment

Variables	LLFS	FamHS-total	FamHS-random	FamHS-high risk
Individuals (families)*	4572 (581)	4107	1806 (454)	2301 (461)
Age (SD), y	70.26 (15.7)	50.52 (13.17)†	51.54 (13.5)†	49.72 (12.86)†
Sex (%, men)	2068 (45.23%)	1940 (47.24%)	870 (48.17%)‡	1070 (46.5%)
CHD (%, yes)	537 (11.75%)	561 (13.66%)§	140 (7.75%)†	421 (18.3%)†
T2D (%, yes)	400 (8.75%)	617 (15.02%)†	149 (8.25%)	468 (20.34%)†
Hypertension (%, yes)	3090 (67.59%)	1248 (30.39%)†	420 (23.26%)†	828 (35.98%)†
HDL-C (SD), mmol/L	1.53 (0.45)	1.29 (0.38)†	1.30 (0.40)†	1.27 (0.37)†
LDL-C (SD), mmol/L	3.09 (0.92)	3.24 (0.90)†	3.18 (0.89)‖	3.28 (0.92)†
WC (SD), cm	94.72 (13.59)	97.64 (15.27)†	97.49 (15.09)†	97.77 (15.43)†
Smoking (%, yes)	324 (7.09%)	968 (23.57%)†	281 (15.56%)†	687 (29.86%)†
Drinking (%, yes)	2394 (52.36%)	2384 (58.05%)†	932 (51.61%)	1452 (63.1%)†

Mean (SD) or the number of individuals (percentage) is shown.

CHD indicates coronary heart disease; FamHS, Family Heart Study; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LLFS, Long Life Family Study; T2D, type 2 diabetes; and WC, waist circumference.

*Maximum sample size based on the model with age, sex, and CHD.

Comparison between LLFS with each FamHS cohort: †$P<1\times10^{-4}$; ‡$P=0.03$; §$P=0.007$; and ‖$P=2\times10^{-4}$.

176-SNP PRS are shown in Figures II and III in the Data Supplement for LLFS and FamHS, respectively. The means of standardized PRS were significantly ($P<1\times10^{-4}$) different between LLFS with FamHS-high risk and with FamHS-random and between individuals with and without CHD in each cohort (Table III in the Data Supplement). The empirical cumulative distribution function (Figure IV in the Data Supplement) also indicated that the cumulative CHD by PRS was slightly higher in FamHS-high risk compared with FamHS-random and with LLFS.

The CHD frequencies were significantly different between men and women within the same PRS percentile groups ($P\leq1\times10^{-4}$) in each study, where CHD was more prevalent in men than in women (Table III in the Data Supplement). In LLFS, the age-at-onset mean for CHD was significantly different between the first PRS quartile compared with the fourth for men (75.1 for <25%, 69.7 for >75%, $P=0.008$) but not for women (76.4 versus 77.6, $P=0.70$). There were no significant differences in the age-at-onset means for CHD between sexes in FamHS-random or FamHS-high risk. Figure 1 displays the plots of density by PRS and density by CHD age-at-onset for LLFS, FamHS-random, and FamHS-high risk cohorts in men and women. The bimodal distributions in age reflect 2 generations, parents and their offspring. Figure 1 shows the boxplots of PRS percentiles for individuals with and without CHD.

PRSs Contribute to CHD in 3 Family-Based Ascertainments

Association Between PRS With CHD Age-at-Baseline

We first evaluated whether the 176-SNP PRS could predict CHD prevalence at the first clinical examination (baseline) in each cohort employing generalized estimating equations logistic models. Table IV in the Data Supplement contains the association results between PRS with CHD age-at-baseline. PRS were significantly associated with CHD at baseline in FamHS-total population (odds ratio [OR], 1.49; $P=1.82\times10^{-10}$), as well as in FamHS-random (OR, 1.50; $P=4.86\times10^{-4}$) and FamHS-high risk for CHD (OR, 1.39; $P=1.98\times10^{-5}$), as expected. The association of PRS with CHD also occurred in the healthy-aging LLFS families (OR, 1.40; $P=4.79\times10^{-10}$).

Sex-stratified association differences were apparent for both FamHS cohorts but not for LLFS. There was a similarly significant association of PRS with CHD at baseline in LLFS men (OR, 1.49; $P=1.60\times10^{-9}$) and women (OR, 1.27; $P=3.59\times10^{-3}$). In contrast, a significant association was present in men for FamHS-high risk (OR, 1.58; $P=8.35\times10^{-6}$) and FamHS-random (OR, 1.56; $P=5.47\times10^{-4}$) but not in women ($P=0.32$ and $P=0.46$, respectively). The PRS remained significantly associated with CHD prevalence even after adding the cardiovascular risk factors in the sex-combined and sex-stratified models (Table IV in the Data Supplement).

Association Between PRS With CHD Age-at-Onset

To determine whether individuals within PRS percentile groups had similar CHD age-at-onset in LLFS compared with FamHS cohorts, we employed the Kaplan-Meier method and Cox regression hazard models. Figure 2 depicts the Kaplan-Meier plot of the CHD probability of remaining free of CHD by age-at-onset for PRS extreme quartile distributions in men and women (Table V in the Data Supplement). The rank tests of equality over strata indicated significant differences ($P<1.0\times10^{-17}$) between the cohort groups in sex-combined family members,

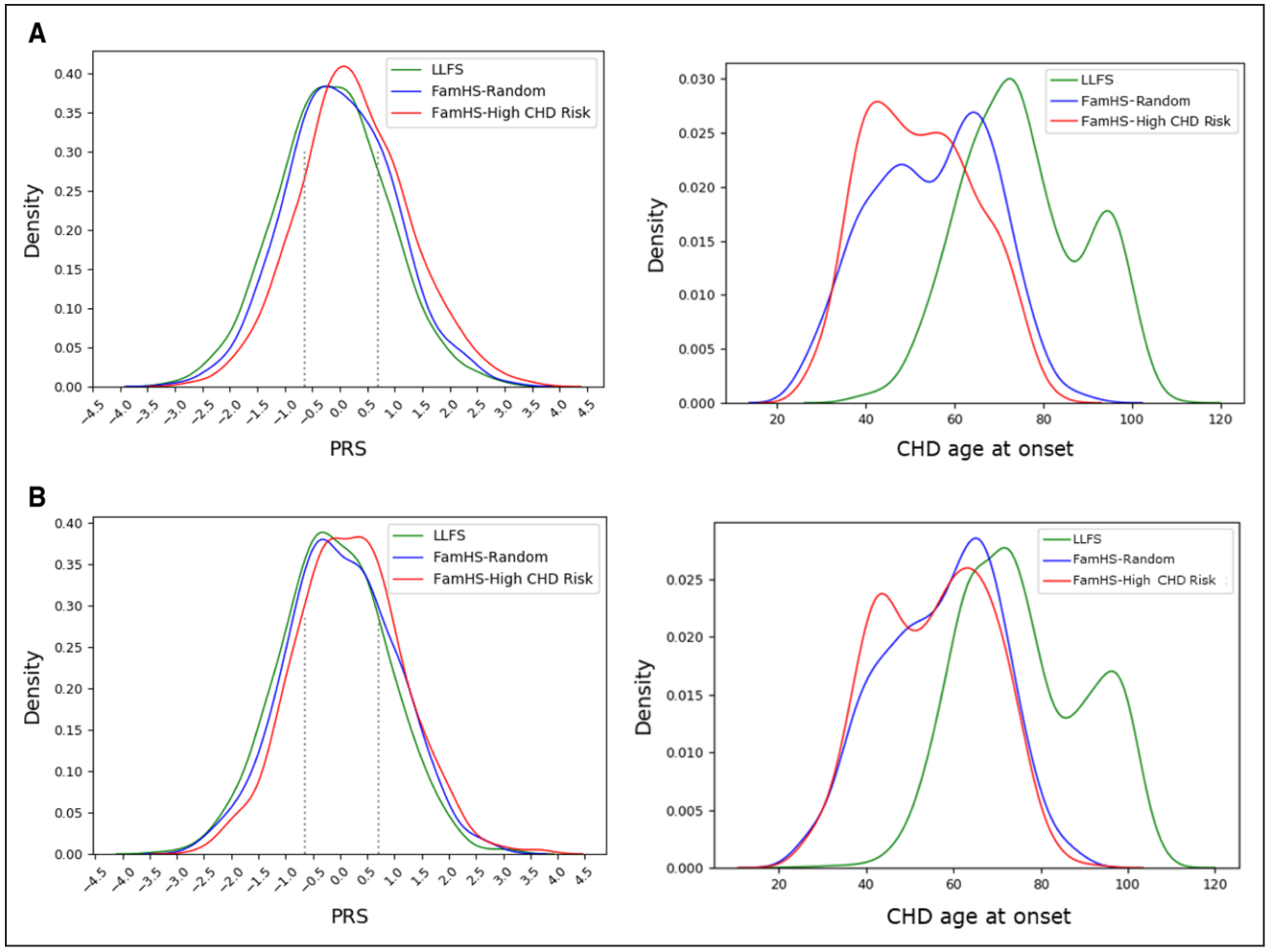

Figure 1. Density plots for polygenic risk scores (PRS) and coronary heart disease (CHD) age-at-onset by sex and family ascertainment.

The vertical lighter dotted lines refer to PRS 25th percentile and 75th percentile, in men (**A**) and women (**B**). FamHS indicates Family Heart Study; FamHS-random, randomly selected FamHS families; FamHS-high risk, high CHD risk FamHS families; and LLFS, Long Life Family Study.

men, and women. The CHD-free probability by age-at-onset was significantly ($P_{Šidák}$ <1.0×10^{-2}) delayed in LLFS compared with FamHS-high risk in both sexes. The CHD age-at-onset was also delayed in LLFS compared with FamHS-random, except for LLFS PRS >75% with FamHS-random PRS <25% for combined and stratified sexes and with PRS >75% in women (P>0.05).

To test whether the trends in scores across the groups were not an artifact of unaccounted for correlations between family members, we employed Kaplan-Meier's method in unrelated individuals and Cox regression hazard model with replacement family bootstrap sampling. Even though the sample size dropped 80% (1496 unrelated individuals), the rank tests of equality over strata were significant between the cohort groups, in sex-combined (P<1.0×10^{-17}), men (P<1.0×10^{-17}), and women (P=4.99×10^{-9}). Kaplan-Meier's results suggested that CHD age-at-onset differed between groups, FamHS-high risk (the PRS >75%) with LLFS (PRS <25%, $P_{Šidák}$=0.006) and with FamHS-random (PRS <25%, $P_{Šidák}$=0.002 and PRS >75%, $P_{Šidák}$=0.0021).

The Cox regression hazard model with replacement family bootstrap sampling confirmed Kaplan-Meier results, demonstrating delayed CHD age-at-onset in LLFS compared with FamHS cohorts. Table 2 summarizes these Cox regression results for CHD age-at-onset differences between PRS percentile groups between LLFS with both FamHS cohorts. The delayed CHD age-at-onset between LLFS with FamHS-high risk increased from the first to the fourth PRS quartile (HR, 0.48; P=6.5×10^{-7} to HR, 0.13; P<1.0×10^{-17}, respectively).

Additionally, we performed Cox proportional hazard models to investigate the CHD age-at-onset relationship with PRS and family ascertainment (LLFS, FamHS-random, and FamHS-high risk) 3-level categorical overall class variable, using the Wald test. To correct for traditional cardiovascular factors, we included baseline age, sex, type 2 diabetes, hypertension, HDL-C, LDL-C, waist circumference, smoking, and drinking in the model (Table VI in the Data Supplement). We found significant associations of CHD age-at-onset with PRS (P=1.46×10^{-17}), 3-level family ascertainment (P<1.0×10^{-17}), sex (P<1.0×10^{-17},

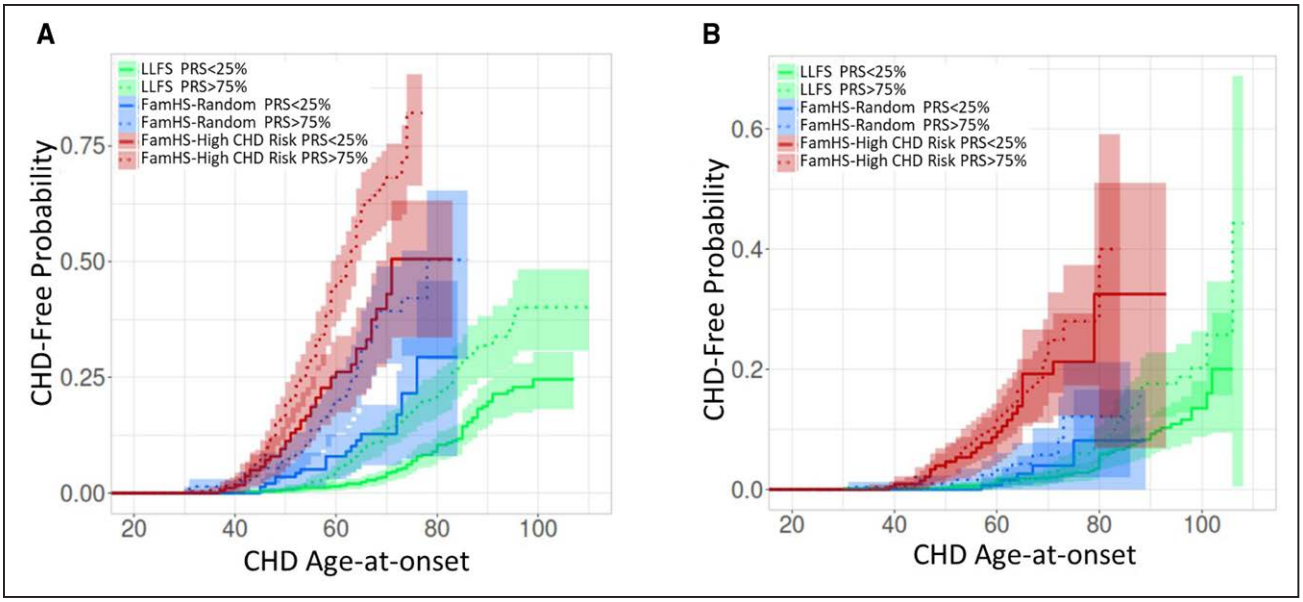

Figure 2. Kaplan-Meier plots of polygenic risk scores (PRS) extreme quartile distributions of coronary heart disease (CHD)-free probability by age-at-onset comparing sex and family ascertainment.
The pairwise comparisons between PRS extreme quartile groups and family ascertainment, in men (**A**) and women (**B**), are shown in Table V in the Data Supplement. FamHS indicates Family Heart Study; FamHS-random, randomly selected FamHS families; FamHS-high risk, high CHD risk FamHS families; and LLFS, Long Life Family Study.

Table VII in the Data Supplement). These findings suggest heterogeneity in 3 family-based ascertainments with low (LLFS), random (FamHS-random), and high CHD risk (FamHS-high risk). To test the differences between the 2 extreme CHD risk families with the random families (ie, FamHS-high risk versus FamHS-random and LLFS versus FamHS-random), we applied Cox proportional hazard model with coxme package. The results confirmed the association of CHD age-at-onset with PRS (HR, 1.35 per SD of PRS; $P<1\times10^{-17}$), LLFS (HR, 0.57; $P=3.8\times10^{-6}$), and FamHS-high risk (HR, 2.98; $P<1.0\times10^{-17}$, Table VIII in the Data Supplement). Due to a significant sex-specific association (HR, 0.42; $P<1.0\times10^{-17}$, Table 3), we tested the effect of PRS interaction with sex in conjunction with other terms in the model. The significant interaction effect (PRS*sex: $P=2.7\times10^{-3}$, Table IX in the Data Supplement) demonstrated that PRS predicted CHD age-at-onset differently in men and women. PRS (HR, 1.57; $P=1.3\times10^{-5}$), LLFS (HR, 0.54; $P=2.6\times10^{-5}$), and FamHS-high risk (HR, 2.86; $P=6.7\times10^{-15}$, Table 3) were significantly associated with CHD age-at-onset in men. In women, there was evidence of CHD age-at-onset to be associated with PRS (HR, 1.76; $P=7.7\times10^{-3}$), FamHS-high risk (HR, 4.88, $P=8.7\times10^{-10}$), and PRS*FamHS-high risk (HR, 0.61; $P=3.6\times10^{-2}$). Even after adjusting for menopause status ($P=1.4\times10^{-3}$, Table X in the Data Supplement) and other cardiovascular risk factors, the association pattern remained similar.

Furthermore, we evaluated whether individuals in both PRS extreme distributions had substantially greater effects on CHD age-at-onset in terms of hazard ratios and *P* values than the whole distribution. The magnitude of parameter estimates increased in women in the extreme PRS quartile groups, even after the sample size was reduced (from 3979 to 1982). There was evidence of CHD age-at-onset to be associated with PRS (HR, 2.74; $P=6.9\times10^{-3}$), FamHS-high risk (HR, 7.23, $P=1.1\times10^{-2}$), and interaction of PRS with low and high familial risk for CHD (PRS*LLFS: HR, 0.46; $P=4.9\times10^{-2}$, and PRS*FamHS-high risk: HR, 0.39; $P=1.8\times10^{-2}$, respectively, Table XI in the Data Supplement). For men, the association pattern of CHD age-at-onset with PRS in the extreme quartiles remained similar to the total sample results. These findings indicated that PRS predict CHD age-at-onset in men and women. There was also a suggestion that PRS interact with their low (LLFS) or high familial risk (FamHS-high risk) for CHD in women.

DISCUSSION

Our study demonstrated that the association of PRS with prevalent CHD depends on the age-at-baseline, age-at-onset, sex, and familial risk for CHD. Sex-specific PRS association with incident CHD was reported in the MESA (Multi-Ethnic Study of Atherosclerosis), in which a 46-SNP PRS was associated with incident CHD in men (N=1206) but not in women (N=1320).[14] The lower CHD in women for MESA, FamHS-high risk, and FamHS-random (6.5%, 10.0%, and 2.9%, respectively) compared with men (11.9%, 27.9%, 13.0%, respectively) at approximately the same age means for both sexes (63, 50, and 52, respectively), could have contributed to the

Table 2. Results for CHD Age-at-Onset Within PRS Percentile Groups*

Group comparisons	N_{Family}	$N_{Individuals}$	χ^2	*P* value	HR (95% CI)
PRS <25% group					
LLFS vs FamHS-random	412	1784	16.04	6.21×10^{-5}	0.37 (0.23–0.60)
LLFS vs FamHS-high risk	555	3181	24.75	6.54×10^{-7}	0.48 (0.36–0.64)
PRS 25%–75% group					
LLFS vs FamHS-random	418	1790	164.52	$<1.0\times10^{-17}$	0.11 (0.08–0.15)
LLFS vs FamHS-high risk	605	3426	210.93	$<1.0\times10^{-17}$	0.17 (0.13–0.22)
PRS >75% group					
LLFS vs FamHS-random	373	1407	38.91	4.44×10^{-10}	0.33 (0.24–0.47)
LLFS vs FamHS-high risk	421	1654	256.42	$<1.0\times10^{-17}$	0.13 (0.10–0.16)

CHD indicates coronary heart disease; FamHS, Family Heart Study; FamHS-high risk, high CHD risk FamHS families; FamHS-random, randomly selected FamHS families; HR, hazard ratio; LLFS, Long Life Family Study; N_{Family}, number of families; and $N_{Individuals}$, number of individuals.

*HR probability (95% CI) of having CHD in LLFS compared with the CHD probability in FamHS-random or FamHS-high risk using 10 000 family bootstrap sampling.

lack of association in women. In LLFS, there was a significant association of PRS with CHD at baseline in men and women. The prevalence of CHD was also lower in women (7.8%) than in men (16.5%). But women in LLFS were older (age-at-baseline means of ≈70.5 years) than in MESA (≈63 years) and FamHS (≈51 years) cohorts. It is well known that men have a higher risk of developing CHD[15] and fatal CHD (up to 84 years)[1] than women. The average age of a first heart attack in women also happens ≈7 years later than in men,[1] and the age differences of the first manifestation for CHD between men and women decay during the lifetime.[16] In a prospective population-based cohort study, the first CHD incident manifestation at age 55 was 27.2% in men and 16.9% in women and decreased to 15.4% men and 12.5% in women at age 75.[16] The observed sex differences in the CHD prevalence and presentation might partially reflect the distinct pathophysiological processes, which lead to higher myocardial ischemia in men than women. They are more predisposed to have an impaired coronary vasomotor function and microcirculatory dysfunction than men.[17] Myocardial infarction in young-middle-aged women is often neglected with atypical symptoms, such as epigastric pain, dyspepsia, or breathlessness,[18] which might also explain part of the lack of PRS and CHD age-at-baseline association in women.

Participants in LLFS presented a significant delay of ≈17 years for CHD age-at-onset than FamHS cohorts in the high PRS (>75%) distribution. A previous study with LLFS individuals had shown better health, cardiovascular-related phenotypes, and physiological function than other cohorts with similarly aged individuals.[12] These findings demonstrated that PRS captured part of the CHD age-at-onset differences in individuals with low or high genetic risks for CHD from distinct ascertained family-based ascertainments (LLFS and FamHS-high risk).

The medians of PRS percentile scores were higher in men and women with CHD versus without CHD in FamHS-high risk (69 versus 65 and 65 versus 43, respectively, Figure 3), and both PRS percentile medians from FamHS-high risk were higher than in LLFS (60 versus 58 and 51 versus 47, respectively). LLFS participants also had lower PRS percentile medians compared with the ones reported in the large UK Biobank (N≈289 K), in which the median PRS (>6 M variants) percentile score was 69 for individuals with CHD versus 49 for individuals without CHD.[19] It is worth noting that in the extreme PRS quartile distributions (Table XII in the Data Supplement), 58.6% of women from the healthy-aging LLFS families were at the lowest genetic risk for CHD (PRS <25%). In comparison, 59.2% of women from the FamHS-high risk families for CHD were in the highest genetic risk category (PRS >75%). Figure 3 shows that for extreme PRS distributions, the median PRS percentile score for women without CHD was much lower in LLFS (≈20%) compared with FamHS-high risk (≈80%). In comparison, the median PRS percentile scores for women with CHD were similar in both family data (≈80%). These findings indicate that PRS percentile medians were elevated in the CHD risk groups and might help to categorize individuals into high versus low genetic CHD risk for the disease. However, the interquartile PRS percentile ranges (represented by non-CHD and CHD boxes in Figure 3) demonstrated that PRS could not define a threshold between individuals with or without CHD. Although individuals from LLFS had on average delayed CHD age-at-onset, a subset of participants had high PRS values. Likewise, there were individuals from the FamHS-high risk who had low PRS levels. These findings suggest that genetic risk contributes to CHD, but it may not be enough to cause the disease. Genetic effects are likely modulated by other factors, such as lifestyle and environment.

We identified significant CHD age-at-onset associated with a family history of low CHD risk (LLFS), high CHD risk (FamHS-high risk), and their interactions with PRS in women after correcting for traditional cardiovascular risk factors. In men, PRS and family-based ascertainments for CHD were the primary determinants

Table 3. Results for CHD Age-at-Onset With PRS, Sex, Family Ascertainment, and Interaction Terms Corrected by Cardiovascular Risk Factors

	Total (Sex-combined)*		Men		Women	
Variables	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
PRS	1.60 (1.33–1.92)	3.9×10^{-7}	1.57 (1.28–1.92)	1.3×10^{-5}	1.76 (1.16–2.68)	7.7×10^{-3}
Age	0.95 (0.94–0.96)	$<1\times10^{-17}$	0.94 (0.93–0.95)	$<1\times10^{-17}$	0.96 (0.95–0.97)	2.2×10^{-9}
Sex	0.42 (0.36–0.5)	$<1\times10^{-17}$				
LLFS	0.61 (0.48–0.78)	8.2×10^{-5}	0.54 (0.41–0.72)	2.6×10^{-5}	0.91 (0.54–1.54)	7.2×10^{-1}
FamHS-high risk	3.20 (2.54–4.04)	$<1\times10^{-17}$	2.86 (2.2–3.73)	6.7×10^{-15}	4.88 (2.94–8.1)	8.7×10^{-10}
PRS*LLFS	0.82 (0.67–1.01)	6.6×10^{-2}	0.87 (0.69–1.1)	2.5×10^{-1}	0.66 (0.42–1.04)	7.5×10^{-2}
PRS*FamHS-high risk	0.81 (0.66–1.01)	6.1×10^{-2}	0.90 (0.71–1.15)	4.2×10^{-1}	0.61 (0.38–0.97)	3.6×10^{-2}
T2D	1.96 (1.64–2.35)	3.3×10^{-13}	1.90 (1.52–2.37)	1.3×10^{-8}	2.28 (1.64–3.17)	9.0×10^{-7}
Hypertension	1.52 (1.3–1.77)	1.3×10^{-7}	1.42 (1.18–1.71)	1.6×10^{-4}	1.63 (1.21–2.19)	1.3×10^{-3}
HDL-C	0.98 (0.98–0.99)	9.0×10^{-12}	0.98 (0.97–0.99)	4.8×10^{-7}	0.98 (0.97–0.99)	1.1×10^{-4}
LDL-C	1.00 (0.99–1)	2.80×10^{-6}	0.99 (0.99–1)	6.8×10^{-5}	0.99 (0.99–1)	1.1×10^{-3}
WC	1.00 (1–1.01)	4.40×10^{-1}	1.00 (0.99–1.01)	7.4×10^{-1}	1.00 (1–1.01)	2.8×10^{-1}
Smoking	1.18 (0.94–1.49)	1.50×10^{-1}	1.18 (0.9–1.55)	2.3×10^{-1}	1.22 (0.77–1.92)	4.0×10^{-1}
Drinking	0.99 (0.86–1.14)	8.70×10^{-1}	1.02 (0.86–1.21)	8.0×10^{-1}	0.99 (0.76–1.29)	9.5×10^{-1}

Smoking denotes current cigarette smoking, and drinking denotes current alcohol drinking. CHD indicates coronary heart disease; FamHS, Family Heart Study; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; LLFS, Long Life Family Study; PRS, polygenic risk scores; T2D, type 2 diabetes; and WC, waist circumference.

*Sample sizes are 7403, 3424, and 3979 individuals (1471, 1244, and 1247 families) for total, men, and women, respectively.

of CHD age-at-onset. Family health history has been reported as a strong predictor of CHD risk.[9–11] It is well known that family members share genetic and common environmental factors that predispose them to develop CHD. However, it remains unclear how genetic risks and family health history mediate CHD. Currently, few sex-specific CHD GWAS have been reported, which may partially be due to the sex differences in CHD manifestations (ie, progression, presentation, age-at-onset) that are primarily based on male standards. These may result in lower specificity and accuracy of CHD outcomes in women.[20] However, sex-specific genetic effects on CHD have been described in gene candidates, warranting further sex-specific PRS investigations.[20]

Additional future directions for this work include identifying SNPs associated with CHD from large multi-ancestry GWAS, including sex-specific SNPs, which may improve the discrimination of risk and prevention for CHD. Large-scale whole-genome sequencing studies that identify SNPs with low-rare minor allele frequencies and high effect sizes will further provide deeper and more comprehensive coverage of the genome. Improving the relative genetic risk of CHD will likely enhance the discrimination among individuals in the extreme PRS distributions and may have significance in determining the causes of CHD. Those at the highest genetic risk might have a greater benefit from early therapeutic intervention and changes in their lifestyle to prevent CHD events. Whole-genome sequencing might also help identify protective variants for CHD age-at-onset, carried from healthy-aging family individuals, with potential genomic medicine applications.

Strengths and Limitations

Our study employed a unique approach of CHD age-at-onset by using PRS among 3 prospective family-based ascertainments recruited with varying familial enrichment of CHD risk. Our analyses demonstrated the sex-specific effects of PRS on CHD age-at-onset and interactions of PRS with familial risk for CHD in women. However, several limitations are worth mentioning.

First, our analyses were performed in European ancestry individuals, where most of the GWAS meta-analyses have been undertaken to date. Nonetheless, differences in linkage disequilibrium patterns, allele frequencies, and effect sizes of the 176-SNP PRS generated here might not have the optimal predictive impact in other ancestry populations.

Second, CHD treatments (eg, statin, anticoagulant, beta-blocker, antianginal, and calcium channel blocker) and lifestyle changes over time were not considered in our models, which could have influenced our results. However, our models included baseline measures of traditional cardiovascular factors (type 2 diabetes, hypertension, HDL-C, LDL-C, menopause status, waist circumference, smoking, and drinking), which might account for some of the correlation between CHD covariate effects and mitigate some collinearity.

Third, LLFS and FamHS do not have information on family members who died of CHD before baseline (in visit 1) or LLFS family members who died in their 50's or 60's when they were of similar age as FamHS. Consequently, we do not have the death age overlap between studies to evaluate whether there might be a

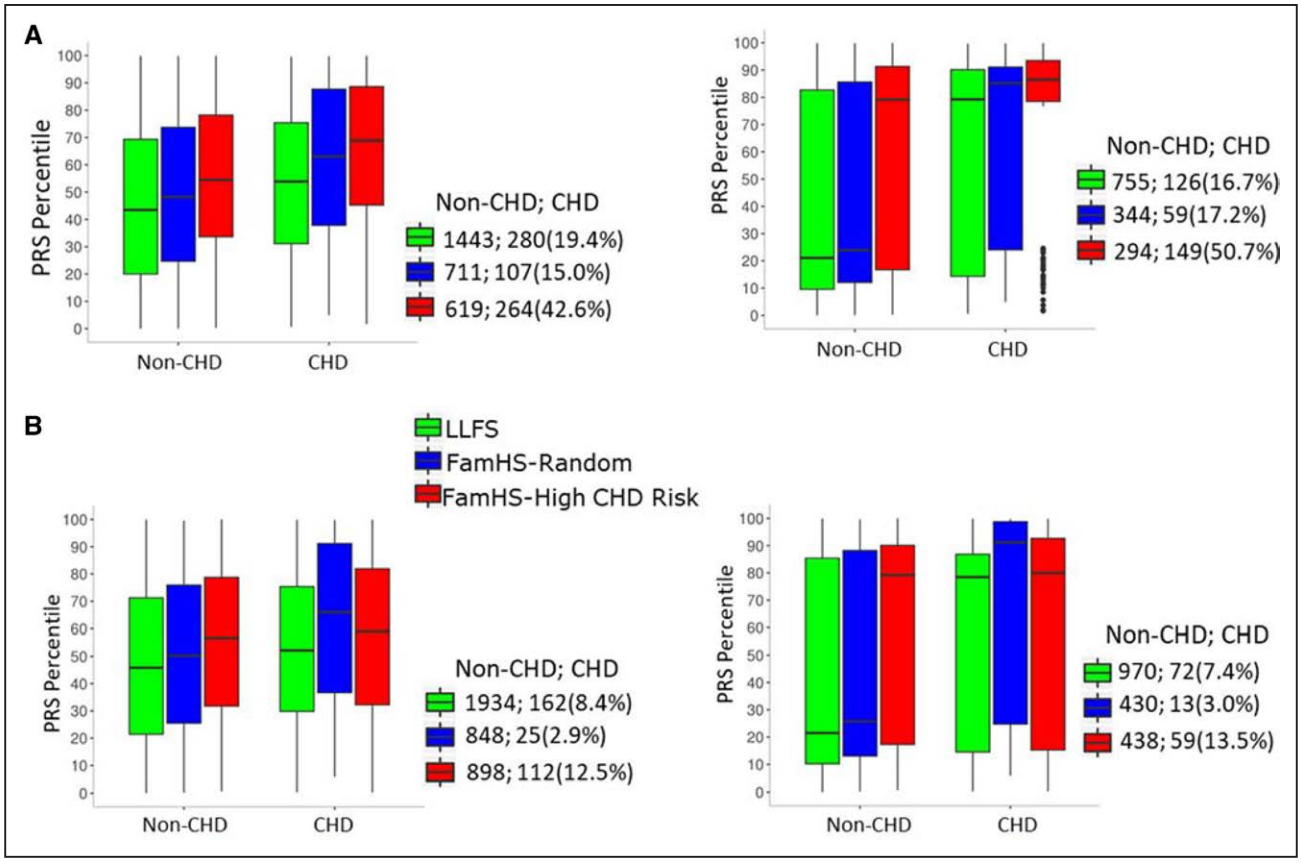

Figure 3. Boxplots of polygenic risk scores (PRS) percentiles for coronary heart disease (CHD) versus non-CHD in LLFS (Long Life Family Study), randomly selected FamHS families (FamHS-random), and high CHD risk FamHS families (FamHS-high risk). Individuals of overall (in the left) or extreme (<25% and >75%, in the right) PRS distributions.
In each boxplot shown for men (**A**) and women (**B**), the horizontal line represents the median, the **top** and **bottom** represent the interquartile range, and the whiskers represent the maximum and minimum PRS values.

contribution of survivor bias or exceptionality healthy individuals in LLFS. However, Newman et al[12] demonstrated that LLFS participants were generally healthier than similarly aged cohorts.

Fourth, PRS assumed that each allele had a linear additive effect, without epistatic interactions or pleiotropic relationships with CHD-related phenotypes that may improve PRS accuracy and CHD risk discrimination. However, our models may account for part of the pleiotropy among CHD-related phenotypes through inherent shared family history for CHD risk within cohorts.

Fifth, the SNPs associated with CHD prevention (ie, with low CHD genetic risk) may have been missed from our PRS, which were generated from large GWAS meta-analyses aimed to identify risk loci. Similarly, GWAS focus on common variants and, therefore, rare variants with large effect are not included in our PRS. The inclusion of such variants would likely enhance the ability to separate the individuals of the healthy-aging LLFS from the FamHS-high risk families.

Finally, the statistical analyses for trends or associations of uncensored-censored CHD age-at-onset with PRS have some advantages and disadvantages but the analyses complement each other. The Kaplan-Meier method does not account for family relatedness. Still, it allows testing the probability that there is a trend in scores across the groups that can be graphically represented. Cox regression hazard models with replacement family bootstrap sampling do not provide a graphical representation; however, they offer unbiased familial estimates of the scores' trends across the groups. The Cox proportional hazard model with a coxme package allows for testing complex models; however, our sample sizes were relatively small to use a finer PRS quantile. Despite that, our data had enough power for tailoring the PRS distribution to its extreme quartiles, providing evidence of interactions of PRS with family-based ascertainments (LLFS and FamHS-high risk) on CHD age-at-onset in women, accounting for cardiovascular risk factors. Even with the small sample size, our study revealed significant findings in the main effect and interaction analyses; however, further investigations from independent studies are needed to confirm our discoveries.

Conclusions

There is evidence of interaction between PRS with sex modulating CHD age-at-onset, corrected for cardiovascular risk factors. PRS and CHD family history were the major effects on the CHD age-at-onset in men. In women, the CHD age-at-onset was associated with PRS, CHD family history, and interactions of PRS with CHD family history. PRS, sex, age-at-onset, and family health history captured some risks to predict prevalent CHD, which may lead to more personalized medicine. Identifying individuals at high risk for CHD may provide benefits for an early therapeutic intervention and changes in their lifestyle to prevent CHD events.

ARTICLE INFORMATION

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Affiliations

Division of Statistical Genomics, Department of Genetics, Washington University School of Medicine, St. Louis, MO (M.F.F., M.K.W., L.W., M.A.P.). Department of Epidemiology (A.L.K., E.B.-M., A.B.N., J.M.Z.) and Department of Human Genetics (J.M.Z.), University of Pittsburgh, PA. Biodemography of Aging Research Unit, Social Science Research Institute, Duke University, Durham, NC (A.M.K.). Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis (B.T.). Sergievsky Center, Taub Institute, Department of Epidemiology and Department of Neurology, Columbia University, NY (J.H.L.). Department of Medicine, Boston University School of Medicine, MA (T.P.). Danish Aging Research Center, University of Southern Denmark, Odense C (K.C.).

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Disclosures

None.

Supplemental Materials

Supplemental Methods
Supplemental Tables I–XII
Supplemental Figures I–IV
References [21–23]

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