

ORIGINAL ARTICLE

Prognostic Value of a Polygenic Risk Score for Coronary Heart Disease in Individuals Aged 70 Years and Older

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BACKGROUND: The use of a polygenic risk score (PRS) to improve risk prediction of coronary heart disease (CHD) events has been demonstrated to have clinical utility in the general adult population. However, the prognostic value of a PRS for CHD has not been examined specifically in older populations of individuals aged ≥ 70 years, who comprise a distinct high-risk subgroup. The objective of this study was to evaluate the predictive value of a PRS for incident CHD events in a prospective cohort of older individuals without a history of cardiovascular events.

METHODS: We used data from 12 792 genotyped, healthy older individuals enrolled into the ASPREE trial (Aspirin in Reducing Events in the Elderly), a randomized double-blind placebo-controlled clinical trial investigating the effect of daily 100 mg aspirin on disability-free survival. Participants had no previous history of diagnosed atherothrombotic cardiovascular events, dementia, or persistent physical disability at enrollment. We calculated a PRS (meta-genomic risk score) consisting of 1.7 million genetic variants. The primary outcome was a composite of incident myocardial infarction or CHD death over 5 years.

RESULTS: At baseline, the median population age was 73.9 years, and 54.9% were female. In total, 254 incident CHD events occurred. When the PRS was added to conventional risk factors, it was independently associated with CHD (hazard ratio, 1.24 [95% CI, 1.08–1.42], $P=0.002$). The area under the curve of the conventional model was 70.53 (95% CI, 67.00–74.06), and after inclusion of the PRS increased to 71.78 (95% CI, 68.32–75.24, $P=0.019$), demonstrating improved prediction. Reclassification was also improved, as the continuous net reclassification index after adding PRS to the conventional model was 0.25 (95% CI, 0.15–0.28).

CONCLUSION: A PRS for CHD performs well in older people and improves prediction over conventional cardiovascular risk factors. Our study provides evidence that genomic risk prediction for CHD has clinical utility in individuals aged 70 years and older.

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Key Words: aspirin ■ cardiovascular disease ■ genetics ■ prognosis ■ risk factor

An increasing number of recent studies have suggested the potential clinical utility of using a polygenic risk score (PRS) to improve the prediction of coronary heart disease (CHD) events in the general

population.^{1–8} It is now well established that adults with a high genetic risk score will have higher risk for CHD events, compared to those with a low score.³ Furthermore, the addition of a PRS has been shown to significantly

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Nonstandard Abbreviations and Acronyms

ASPREE	Aspirin in Reducing Events in the Elderly
CHD	coronary heart disease
HDL	high-density-lipoprotein
PRS	polygenic risk score

improve CHD risk prediction when added to a risk model comprised of conventional risk factors.⁴ Notably, a PRS comprising 1.7 million variants (meta-genomic risk score [metaGRS]) has been shown to increase CHD risk with a HR of 1.7 per SD among >450 000 adults from the general UK population (mean age 56.6 years).⁴ Additional independent validation studies of the metaGRS have also shown consistent performance for CHD risk prediction,^{5–11} including in ethnically diverse populations.^{5,6}

The use of genomics in CHD risk prediction has important clinical implications, given the burden of CHD remains high in most countries, despite significant improvements in prevention and treatment. Improved approaches to risk prediction and early intervention may help to address the burden of CHD, and genomics presents a new opportunity. However, prior studies investigating a genomic risk score for CHD risk prediction have mostly included individuals with a mean age ranging from 50 to 60 years or younger. The use of PRS as a risk factor for CHD has not previously been investigated specifically in older individuals ≥ 70 years, who are themselves a distinct high-risk population.

In addition to the potential differences in PRS performance, older individuals may also require customized CHD risk prediction models with regards to conventional clinical risk factors.¹² Prediction models used to estimate the risk of future CHD events are usually derived from younger populations and based on conventional risk factors, such as blood pressure, diabetes, smoking, or blood lipids.^{13,14} These risk models do not fully explain individual risk in older people and are not recommended for clinical usage in patients aged ≥ 70 years. They require calibration based on data from studies of older individuals. Here, we sought to investigate the prognostic value of a recently derived PRS for CHD in a population of older individuals without a history of CHD events, when added to a conventional risk factor model which we constructed, and also in comparison with the Systematic Coronary Risk Evaluation 2-Older People (SCORE2-OP) risk score, specifically optimized for prediction of cardiovascular events in older people.¹⁵ The objective of our study was to determine whether the potential clinical utility of a PRS for CHD would extend to older individuals aged 70 years and older.

METHODS

The full methods are available in the supplemental material. Requests for data access will be via the ASPREE Principal

Investigators with details for applications provided through the website, www.ASPREE.org. The study was approved by local Ethics Committees and registered on Clinicaltrials.gov. All participants provided informed written consent.

RESULTS

Baseline Characteristics

The median age of the 12 792 genotyped participants was 73.9 years (interquartile range 71.7, 77.3, Table 1); 7027 (54.9%) were female, 391 (3.1%) were current smokers, and 1186 (9.3%) had diabetes. Comparing the 12 792 genotyped participants with nongenotyped participants of the ASPREE trial, we found only minor differences in baseline characteristics (Table S1 in the [Supplemental Material](#)). The PRS showed a normal distribution (Figure S3 in the [Supplemental Material](#)), and the mean value was -1.16 (SD, 0.45). There was no relevant correlation of the PRS with other continuous variables within the data set (Figure S4 in the [Supplemental Material](#)). In a multivariable linear regression model, the PRS was significantly associated with age, gender, systolic blood pressure, non-HDL (high-density lipoprotein) cholesterol, HDL cholesterol, diabetes, and family history of MI (Table S2 in the [Supplemental Material](#)). During follow-up, 254 (2.0%) of genotyped participants had incident CHD events (169 in males, 85 in females). This included 226 incident cases of myocardial infarction and

Table 1. Baseline Characteristics

	Overall population
No. of participants	12 792
Age, median (IQR)	73.9 (71.7–77.3)
Age categories (%)	
70–74	7698/12 792 (60.2)
75–79	3271/12 792 (25.6)
80–84	1414/12 792 (11.1)
>85	409/12 792 (3.2)
Female (%)	7027/12 792 (54.9)
Current smoker (%)	391/12 792 (3.1)
Systolic blood pressure, mm Hg, mean (SD)	139.46 (16.27)
Diastolic blood pressure, mm Hg, mean (SD)	77.17 (9.97)
Diabetes (%)	1186/12 792 (9.3)
Body mass index, kg/m ² , mean (SD)	27.97 (4.55)
HDL-c, mmol/L, mean (SD)	1.59 (0.46)
Non-HDL-c, mmol/L, mean (SD)	3.69 (0.93)
Fasting Glucose, mg/dL, mean (SD)	98.29 (17.12)
Creatinine, mg/dL, mean (SD)	0.90 (0.22)
Family history of MI (%)	340/12 792 (2.7)
Polygenic Risk Score, mean (SD)	-1.16 (0.45)

Missing values for continuous variables were: 341 for creatinine, 331 for non-HDL-c, 330 for HDL-c, 250 for fasting glucose, and 56 for body mass index. IQR indicates interquartile range, HDL-c, high-density lipoprotein cholesterol; and MI, myocardial infarction.

50 cases of CHD death. The incidence rate was 3.11 CHD events per 1000 person-years in PRS tertile 1, 4.29 CHD events per 1000 person-years in PRS tertile 2, and 4.97 CHD events per 1000 person-years in PRS tertile 3 (Table 2).

PRS for Risk Prediction

In the conventional model, all variables except systolic blood pressure and diabetes were found to be independent predictors of CHD events (Table 3). When the PRS was added as a continuous variable to the conventional model, it was found to be an independent predictor of outcome (hazard ratio [HR], 1.24 [95% CI, 1.08–1.42], $P=0.002$). The HR of the PRS per SD was comparable to that reported by 5 other published studies of younger adults where the same PRS was used (Table S3 in the [Supplemental Material](#)).

Using PRS tertiles as a predictor, CHD risk increased as the PRS category increased from the first to third tertile. When compared with the first PRS tertile (low-risk group) the second tertile had an HR for CHD risk of 1.48 (95% CI, 1.04–2.09, $P=0.029$) and the third PRS tertile had an HR of 1.64 (95% CI, 1.16–2.33, $P=0.005$). Kaplan-Meier curves illustrated that individuals in the higher and middle PRS tertiles had a higher incidence of CHD events compared with lower PRS tertile ($P=0.02$, Figure 1). Furthermore, the continuous PRS was a significant predictor of outcome, when added to the SCORE2-OP risk model (HR, 1.24 [95% CI, 1.09–1.42], $P=0.001$).

Evaluation of each single predictor using receiver-operating-characteristics showed that sex (area under the curve [AUC], 62.88% [95% CI, 59.58–66.17]), HDL-cholesterol (AUC, 61.56% [95% CI, 57.51–65.61]), serum creatinine (AUC, 61.39% [95% CI, 57.53–65.24]), and age (AUC, 57.50% [95% CI, 52.98–62.05]) were the strongest predictors of incident CHD events (Figure 2). The PRS alone resulted in an AUC of 55.72% (95% CI, 51.74–59.72). The AUC for the conventional model was 70.53% (95% CI, 67.00–74.06) and significantly improved to 71.78% (95% CI, 68.32–75.24) after adding the PRS as a continuous variable ($P=0.019$, Table 4, Figure S5 in the [Supplemental Material](#)). The calibration plot showed a good agreement between predicted and observed CHD events (Figure S6 in the [Supplemental Material](#)). The SCORE2-OP risk model alone resulted in an AUC of 68.32% (95% CI, 64.70–71.94) and

increased to 69.73% (95% CI, 66.17–73.30, $P=0.081$) after adding the continuous PRS.

Reclassification Analyses

In reclassification analyses, the continuous net reclassification improvement was 0.25 (95% CI, 0.15–0.28), when the PRS was added to the conventional model (Table S4 in the [Supplemental Material](#)). More individuals were to a higher risk category (net reclassification improvement+, 0.16, 95% CI, 0.08–0.20), than downwards (net reclassification improvement–, 0.09 [95% CI, 0.04–0.10]). For measurement of the categorical net reclassification improvement, CHD risk categories of <1.5%, <2.5%, and $\geq 2.5\%$ were chosen based on the observed risk within ASPREE (Table S6 in the [Supplemental Material](#), Table 3). Here, addition of the PRS to the conventional model resulted in a categorical reclassification of 0.063 (95% CI, 0.001–0.129), with an upwards classification of 0.044 (95% CI, –0.007 to 0.105) and a downwards classification of 0.019 (95% CI, 0.003–0.032).

Subgroup Analyses

When comparing males and females, we only observed minor differences in baseline characteristics (Table S5 in the [Supplemental Material](#)). Adding the continuous PRS to the conventional model, it was an independent predictor in males, but not in females (males HR, 1.27 [95% CI, 1.08–1.50], $P=0.005$ versus females HR 1.18 [95% CI, 0.92–1.49], $P=0.19$, Tables S6 and S7 in the [Supplemental Material](#)). The same finding was observed when assessing the categorical PRS. The conventional model resulted in a lower AUC in males compared to females (males AUC, 66.58%, females AUC, 70.07%), but the incremental value of adding the PRS to the conventional model was greater in males compared with females (males AUC, 68.18%, females AUC, 71.00%, Table S8 in the [Supplemental Material](#)).

In subgroup analyses by PRS tertile, baseline characteristics were similar for participants within the highest compared to the lowest PRS tertile (Table S9 in the [Supplemental Material](#)). The conventional model resulted in a lower AUC in individuals from the highest, compared to individuals from the lowest PRS tertile (highest tertile AUC, 73.21%, lowest tertile AUC, 76.62%), but the incremental value of addition of the PRS to the conventional model was similar in both groups (Table S10 in the [Supplemental Material](#)).

Results of sensitivity analyses after adding use of antihypertensive drugs, statins, and genetic ethnicity principal component analyses to the model are reported in the supplemental results (Tables S11 and S12 in the [Supplemental Material](#)). Interaction effects between sex and model covariables were examined, but no interaction between sex and PRS was found (HR, 0.93 [95% CI, 0.69–1.24], $P=0.60$; Table S13 in the [Supplemental Material](#)).

Table 2. Incidence Rate of CHD Events Per PRS Tertiles

PRS tertile	N	CHD events	Incidence rate per 1000 person-years
1	4263	56	3.11
2	4264	77	4.29
3	4264	88	4.97

CHD indicates coronary heart disease; and PRS, polygenic risk score.

Table 3. HRs for the Conventional Model, Conventional Model+Continuous PRS, and Conventional Model+Categorical PRS

	Conventional model			Conventional model+ continuous PRS		Conventional model+categorical PRS			SCORE2-OP+continuous PRS			
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Age	1.09	(1.06–1.12)	<0.001	1.09	(1.06–1.12)	<0.001	1.09	(1.06–1.12)	<0.001			
Female sex	0.48	(0.34–0.67)	<0.001	0.46	(0.33–0.65)	<0.001	0.47	(0.34–0.66)	<0.001			
Current smoking	2.00	(1.09–3.68)	0.025	2.02	(1.10–3.71)	0.024	2.01	(1.09–3.69)	0.025			
SBP per 10 mmHg increase	1.04	(0.96–1.13)	0.34	1.04	(0.96–1.13)	0.37	1.04	(0.96–1.13)	0.33			
Non-HDL-c	1.35	(1.17–1.56)	<0.001	1.35	(1.17–1.55)	<0.001	1.34	(1.17–1.55)	<0.001			
HDL-c	0.65	(0.44–0.95)	0.026	0.65	(0.44–0.95)	0.027	0.64	(0.44–0.94)	0.024			
Diabetes	0.82	(0.49–1.38)	0.45	0.81	(0.48–1.36)	0.42	0.81	(0.48–1.36)	0.42			
Creatinine	1.83	(1.03–3.26)	0.040	1.81	(1.01–3.23)	0.045	1.82	(1.02–3.24)	0.043			
SCORE2-OP per 1% risk increase										1.13	(1.10; 1.16)	<0.001
PRS (continuous per SD)				1.24	(1.08–1.42)	0.002				1.24	(1.09; 1.42)	0.001
PRS first tertile							1.00	(Reference)				
PRS second tertile							1.48	(1.04–2.09)	0.029			
PRS third tertile							1.64	(1.16–2.33)	0.005			

HDL-c indicates high-density lipoprotein cholesterol; HR, hazard ratio; PRS, polygenic risk score; SBP, systolic blood pressure; and SCORE2-OP, Systematic Coronary Risk Evaluation 2-Older People.

Finally, we investigated the interaction of aspirin treatment (as per ASPREE randomization) with the PRS but did not find a significant interaction ($P=0.58$, Table S14 in the Supplemental Material).

DISCUSSION

In this study, we evaluated the prognostic value of a previously derived polygenic risk score (metaGRS) to predict future CHD events in a population of healthy older individuals from the ASPREE trial. We demonstrated robust PRS performance in this older population and can confirm that addition of the PRS to a conventional cardiovascular risk model improved risk prediction (Figure 3). Our study suggests that the potential clinical utility of a PRS for CHD risk

prediction extends to older individuals aged 70 years and older, who comprise an important high-risk group. Our study also represents an independent validation of a recently derived PRS, in a well-characterized older population. Our findings add further support to the growing body of evidence that supports the use of genomic risk information to improve CHD risk prediction, and our results indicate that the prognostic value of a genomic risk score for CHD extends to older individuals, who comprise an important high-risk group.

The metaGRS used in our study was derived using data from a range of different CHD studies from younger adult populations, then validated in the UK Biobank population of around 500 000 British individuals, with mean age of 56.5 years.⁴ The score has since been validated in a range of other external validation studies of younger adult

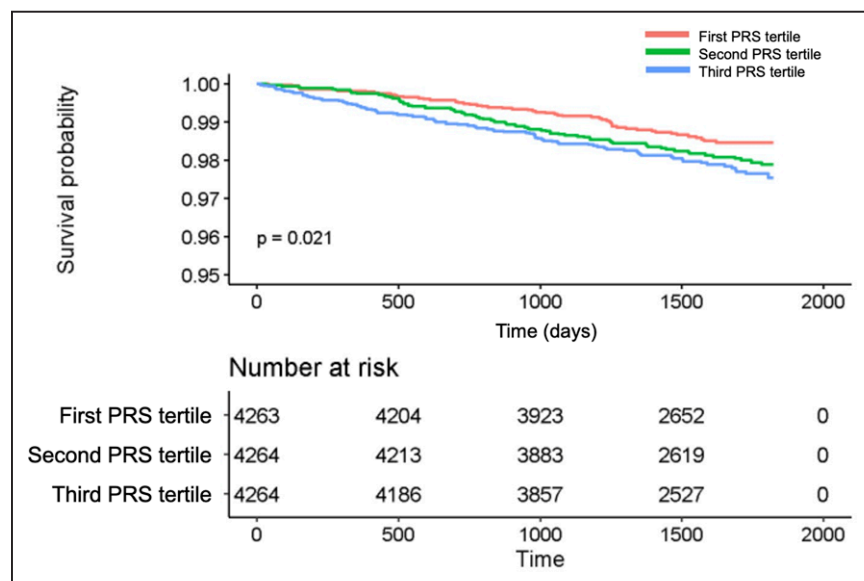


Figure 1. Kaplan-Meier curve for coronary heart disease (CHD) events according to polygenic risk score (PRS) tertiles.

The figure provides the probability of a CHD event according to tertiles of the PRS, based on Kaplan-Meier estimates, and the individuals at risk.

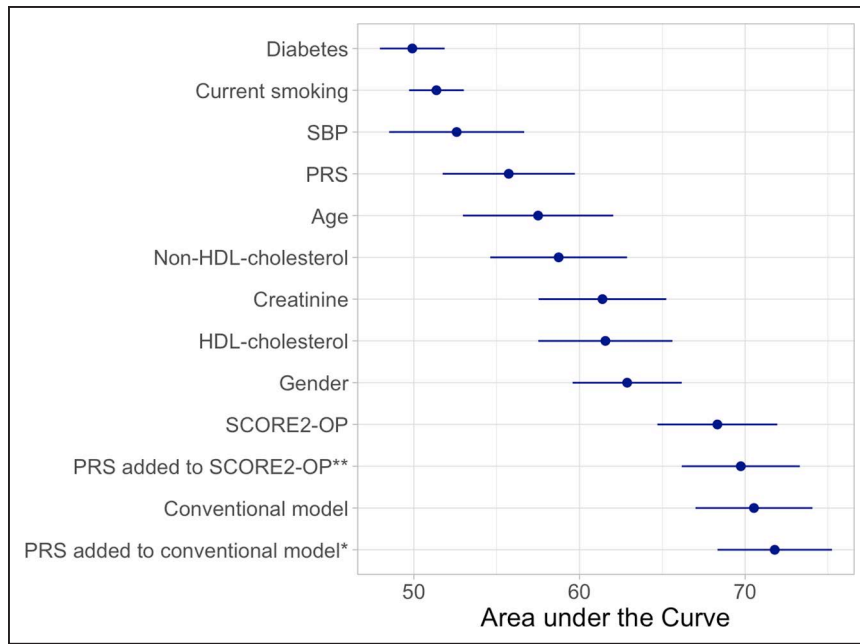


Figure 2. Area under the curve for each predictor, the conventional model, Systematic Coronary Risk Evaluation 2-Older People (SCORE2-OP), and the polygenic risk score (PRS) added to the models.

HDL indicates high-density lipoprotein; and SBP, systolic blood pressure.

*P value compared the Conventional Model=0.019, **P value compared the SCORE2-OP=0.081.

populations (Table S3 in the Supplemental Material).^{5,6,10,11} The ASPREE population differs in several aspects. First, and most notably, the median age of ASPREE participants at enrollment was far older at 73.9 years, nearly 20 years older than the UK Biobank. Yet, the HR of the PRS remained similar. Second, ASPREE is a highly ascertained clinical trial population, in which participants met strict inclusion criteria, with no history of CHD events at enrollment. Third, major CHD events in ASPREE were adjudicated as part of a randomized trial but did not include coronary revascularization. Given these important differences, it is noteworthy that the metaGRS still performed in a robust manner in the older ASPREE population, with similar HR and AUC compared with studies of younger populations. Similar to previous studies,^{5,6} our findings demonstrate a polygenic model derived from the UK Biobank generalizes well to other cohorts of European ancestry.

CHD accounts for a large proportion of deaths in older people. Accurate identification of older individuals at increased risk for CHD is, therefore, clinically important, particularly those not identified as high-risk by conventional risk factors. Due to a lack of evidence in individuals aged 70 years and older, the value of adding genetic information for CHD risk prediction in older people has not previously been tested robustly. Our study, therefore, provides the first evidence of its kind to suggest the predictive value and potential clinical utility of a PRS for CHD extends to individuals aged 70 years and older. We observed comparable predictive performance of the PRS versus younger population-based cohorts^{4-6,10,11} and demonstrated that addition of the PRS to a conventional risk factor model we constructed, and to the recently derived SCORE2-OP clinical risk model, improved prediction.

Table 4. Categorical Net Reclassification Improvement Table After Adding PRS to the Conventional Model to Predict the Risk of a 5-Year CHD Event

	Standard model	Standard model+polygenic risk score			Total no. (%) of participants
		<1.5%	1.5 to 2.49%	≥2.5%	
CHD events	<1.5%	37	9	0	46 (22)
	1.5%–2.49%	6	35	12	53 (25)
	≥2.5%	0	8	103	111 (53)
	Total no. (%) of participants	43 (20)	52 (25)	115 (55)	210 (100)
CHD nonevents	<1.5%	2248	157	2	2407 (49)
	1.5%–2.49%	204	854	149	1207 (25)
	≥2.5%	1	187	1114	1302 (26)
	Total no. (%) of participants	2453 (50)	1198 (24)	1265 (26)	4916 (100)

In this table the reclassification of participants from one risk category (<1.5% risk, 1.5%–2.49% risk, ≥2.5% risk) to another category is described, when adding the Polygenic risk score to the standard model. The table is further by CHD events and CHD nonevents. Light gray shaded boxes indicate the correct reclassification into a different risk category, while dark gray shaded boxes indicate the incorrect reclassification into a different risk category. CHD indicates coronary heart disease; and PRS, polygenic risk score.

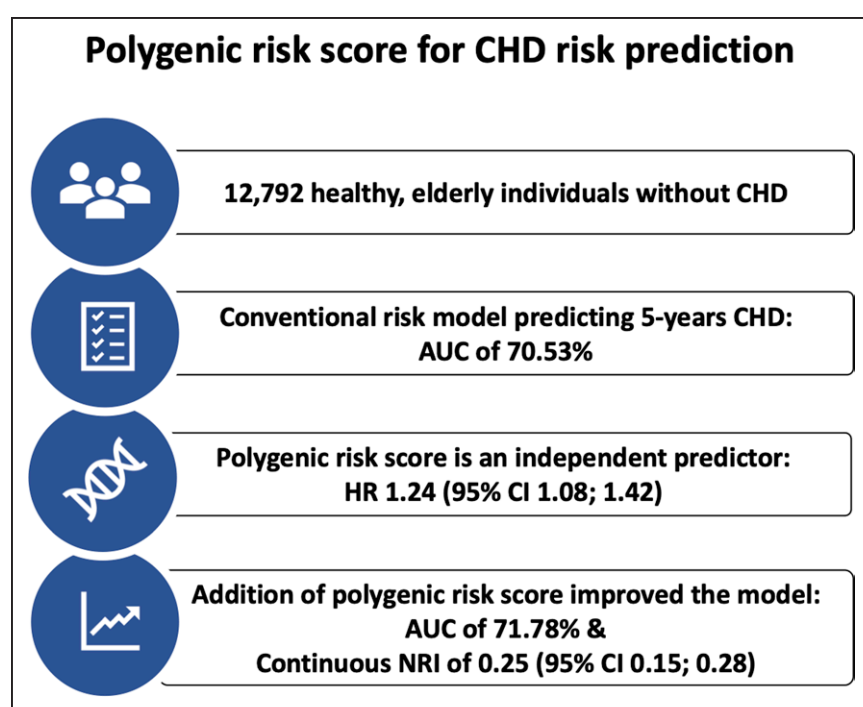


Figure 3. Central figure summarizing the main study findings.

We evaluated the prognostic accuracy of a previously derived polygenic risk score (meta-genomic risk score) to predict 5 y coronary heart disease (CHD) events in a population of healthy elderly individuals. AUC indicates area under the curve; and HR, hazard ratio.

Notably, we found that the PRS alone (considered independently as a CHD risk factor) had similar discriminative power compared to conventional CHD risk factors used in routine practice. However, in our analyses, the AUC of sex, HDL-cholesterol, creatinine, non-HDL-cholesterol, and age were stronger discriminators than the PRS alone. This emphasizes the importance of these risk factors as predictors in an older population, alongside a genetic risk score. Nevertheless, it is noteworthy that the PRS was found to predict CHD events independently of conventional risk factors, not showing correlation with the nine conventional risk factors examined (Figure S4 in the [Supplemental Material](#)). These unique properties of the genetic risk score (ie, relatively strong predictive performance and independent effect) help demonstrate its future clinical potential for CHD risk prediction in populations of older adults.

Currently, the availability of PRS as a clinical tool for CHD prediction at large remains limited, with unresolved questions related to cost-effectiveness and implementation. Furthermore, some recent studies have provided conflicting results regarding the incremental value of adding genetic information to conventional CHD risk factors in younger populations.^{7,8} Although the magnitude of improved CHD risk prediction achieved by the PRS may be small or incremental in an individual study, when the effects are extrapolated to a far larger population (eg, an entire country, comprising millions of older adults), effects are substantial. In the future, individual genotyping will become more widely available and at lower cost, potentially facilitating improved CHD event prediction and risk stratification at the population level. Here, we show that genetic risk is still highly relevant at older ages and that a PRS for CHD still performs well, and may have potential clinical utility

for preventive strategies in older people. However, further studies of more phenotypically and ethnically diverse elderly populations are required to generalize these results.

Specific findings of our study warrant further discussion. First, we did not find diabetes to be an independent predictor for CHD events, despite 9.3% of ASPREE participants having diabetes at baseline. Other studies have reported the relevance of diabetes regarding CHD risk in the elderly.¹² This observation could be explained by the preselection of a healthy ASPREE population, in whom the duration of diabetes might be shorter, compared to the general population. A second notable finding of our study was that results were not confirmed in subgroup analyses for females. This finding was likely due to limited power because the majority of CHD events in ASPREE occurred in males. Further, we found no interaction effect between sex and PRS, and other studies have reported similar performance for CHD polygenic scores in both sexes.¹⁶ Third, we investigated the interaction of aspirin treatment with the metaGRS in exploratory analyses but found no significant interaction ($P=0.58$). This suggested that in the ASPREE trial, participants with a high CHD PRS did not benefit more from low-dose aspirin use, versus participants with a low PRS, for primary prevention of CHD events. Further studies are required to determine whether other genotypic sub-sets of the population may benefit from aspirin use.

Strengths of our study include a well-characterized, unique study population with incident cardiovascular events clinically adjudicated as part of a randomized trial. No other large clinical trial has recruited this number of healthy older individuals without a prior history of CHD events, with genotyping. All ASPREE participants received medical assessments by general practitioners

at enrollment to confirm eligibility for the trial, and to rule out previous diagnoses of CHD events. This provided confidence that participants were CHD event-free at enrollment to examine the value of PRS in the context of primary prevention in the elderly. A range of conventional risk factor variables were also available in ASPREE to examine alongside polygenic risk.

Limitations of our study include a rather short follow-up period (average 4.6 years per participant) contributing to the relatively small number of CHD events. Continued follow-up will provide more power for future analyses. We also acknowledge the potential healthy-volunteer effect (ascertained bias) and survivorship bias of the ASPREE trial population. ASPREE did not collect information related to revascularization, which is an important CHD end point used in metaGRS derivation dataset. Our findings may not be generalizable to other ancestries or more diverse populations.

In conclusion, we report a potential clinical benefit of using a PRS for improved risk prediction of CHD events in older people. Our study provides some of the first evidence that use of PRS for CHD prediction is robust across a diverse range of populations and age groups, including individuals aged 70 years and older which are a distinct high-risk group.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Materials

Supplemental Material
Supplemental Results
Tables S1–S14
Figures S1–S6

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