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Polygenic risk score for breast cancer risk prediction in Asian *BRCA1* and *BRCA2* pathogenic variants carriers

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Polygenic risk scores (PRS) have been shown to be predictive of breast cancer (BC) risk in European *BRCA1* and *BRCA2* pathogenic variant (PV) carriers, but their utility in Asian populations has not been evaluated. In this study, we evaluated the association of two breast cancer PRS developed for the East Asian general population and three versions of a PRS developed for the European general population in 604 *BRCA1* (390 affected by breast cancer) and 785 *BRCA2* (552 affected by breast cancer) PV female carriers of Asian ancestry. Only the Asian-based PRS, constructed using approximately 1 million single-nucleotide variations (SNVs), showed a significant association with breast cancer risk (Hazard Ratio per standard deviation (95% Confidence Interval) is 1.47 (1.10–1.95) for *BRCA1* and 1.43 (1.04–1.95) for *BRCA2*). Incorporating this PRS into risk prediction models may improve cancer risk assessment among PV carriers of Asian ancestry.

Women with pathogenic or likely pathogenic variants (PV) in *BRCA1* or *BRCA2* are at increased risk of developing breast, ovarian and other cancers, and may benefit from risk-management strategies such as risk-reducing medication, risk-reducing surgery, or intensive surveillance[1]. However, the breast cancer risk in *BRCA1* or *BRCA2* PV carriers varies depending on several factors, including genetics, lifestyle and reproductive risk factors, and also depends on the cancer incidence in the population[2–6]. There is a need for accurate risk stratification methods to empower women in making well-informed decisions[7].

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Polygenic risk scores (PRS), combining the effects of multiple disease-associated single nucleotide variations (SNVs), have emerged as powerful tools for breast cancer risk stratification in European populations, both in the general population and *BRCA1* or *BRCA2* PV carriers[3,4,8]. Notably, a PRS developed in the European population using 313 SNVs (PRS_{313}) has shown predictive value for breast cancer risk in Asian populations, albeit with lower discrimination compared to women of European descent[9]. Subsequently, the predictive performance of this European-based PRS was further enhanced by incorporating additional SNVs associated in Asian studies, resulting in a PRS with 333 SNVs (PRS_{333})[10]. Additionally, Ho et al.[10] generated a PRS using a trans-ancestry Bayesian polygenic prediction approach implemented in PRS-CSx[11], resulting in a PRS that includes approximately one million SNVs (PRS_{GW}) and demonstrates the highest predictive accuracy compared to the other two PRS in predicting breast cancer risk in the general Asian populations.

In this study, we aimed to evaluate if these PRS can predict the risk of breast cancer in *BRCA1* and *BRCA2* PV carriers of Asian ancestry.

Results

The study cohort consists of 604 *BRCA1* (390 affected with breast cancer, 96 with ovarian cancer, 118 unaffected with either cancer) and 785 *BRCA2* (552 affected with breast cancer, 46 with ovarian cancer, 187 unaffected) PV carriers recruited from 4 different countries (Supplementary Table S1). The mean age of diagnosis for *BRCA1* PV carriers was 40.9 (SD = 10.2 and for *BRCA2* PV carriers was 44.3 (SD = 10.2), while the mean censoring age for unaffected individuals for *BRCA1* PV carriers was 46.5 (SD = 13.9) and for *BRCA2* carriers was 43.4 (SD = 13.8) (Table 1).

PRS association with breast cancer risk

Five PRS, which were previously demonstrated to be predictive for breast cancer risk in the general Asian population,n were selected for analysis: three based on PRS developed through analyses of studies in the Breast Cancer Association Consortium in European populations[8], and two based on trans-ancestry analyses[9,10] (Supplementary Table S2). We evaluated the association of each PRS with breast cancer risk. The strongest association, in both *BRCA1* and *BRCA2* PV carriers, was with PRS_{GW} (HR = 1.47, 95% CI = 1.10–1.95, $p = 0.0089$ and HR = 1.43, 95% CI = 1.04–1.95, p = 0.0255, respectively) (Table 2). The estimated HRs for the other PRS were greater than 1 but smaller and not statistically significantly different from 1. Sensitivity analysis showed that the hazard ratios for PRS_{GW} were slightly lower and not significant for *BRCA1* (HR = 1.31, 95% CI = 0.94–1.83, $p = 0.1119$) and similar for *BRCA2* PV carriers (HR = 1.44, 95% CI = 1.01–2.07, $p = 0.0457$) when the weights were calculated based on respective country incidence rates rather than using average incidence rates. (Supplementary Table S3).

We further evaluated the association between PRS_{GW} and breast cancer risk when the PRS was treated as a categorical variable. Compared to women in the middle quintile (40–60%), the estimated HRs for developing breast cancer for women in quintiles 1 and 5 were 0.89 (95% CI 0.52–1.52) and 1.57 (0.99–2.49), respectively, for *BRCA1*, and 0.44 (0.24–0.80) and 1.09 (0.67–1.80) (Table 3) for *BRCA2* PV carriers. The estimated HRs by PRS percentile did not differ from those predicted under a theoretical polygenic model in which the log HR depends linearly on the PRS: all predicted HRs fell within the confidence intervals of the observed HRs.

Predicted absolute risk by PRS percentile

We used the hazard ratio estimates and the average breast cancer incidence across the four countries included in this study to compute age-specific absolute cumulative breast cancer risks for PV carriers by PRS percentiles according to PRS_{GW} (Fig. 1). *BRCA1* PV carriers at the 5th percentile of the PRS distribution had an estimated risk of 17% of developing breast cancer by age 50 years and a 38% risk by age 80 years. In contrast, the *BRCA1* PV carriers at the 95th percentile of the PRS distribution had a 45% breast cancer risk by age 50 years and 81% by age 80 years. *BRCA2* carriers at the 5th percentile of the PRS distribution had a risk of 10% of developing breast cancer by age 50 years and a 28% risk by age 80 years. In contrast, *BRCA2*

Table 1 | Description of study cohort

Description	*BRCA1* PV carriers			*BRCA2* PV carriers		
	Total	Aff (%)	Unaff (%)	Total	Aff (%)	Unaff (%)
Total, N	604	390 (100.0)	214 (100.0)	785	552 (100.0)	233 (100.0)
Country						
Malaysia	255	126 (32.3)	129 (60.3)	220	143 (25.9)	77 (33.0)
Korea	218	159 (40.8)	59 (27.6)	359	229 (41.5)	130 (55.8)
Hong Kong	67	52 (13.3)	15 (7.0)	93	74 (13.4)	19 (8.2)
Singapore	64	53 (13.6)	11 (5.1)	113	106 (19.2)	7 (3.0)
Year of Birth						
≤1940	15	6 (1.5)	9 (4.2)	16	15 (2.7)	1 (0.4)
1941-1950	40	22 (5.6)	18 (8.4)	71	58 (10.5)	13 (5.6)
1951-1960	127	86 (22.1)	41 (19.2)	193	140 (25.4)	53 (22.7)
1961-1970	172	118 (30.3)	54 (25.2)	256	189 (34.2)	67 (28.8)
>1970	250	158 (40.5)	92 (43.0	249	150 (27.2)	99 (42.5)
Censoring age						
Mean (SD)	42.9 (12.0)	40.9 (10.2)	46.5 (13.9)	44.1 (11.4)	44.3 (10.2)	43.4 (13.8)
Range	19.13-80.91	19.73–73.63	19.13–80.91	19.19–80.94	22.74–77.77	19.19–80.94
Censoring age group						
≤30	74	45 (11.5)	29 (13.6)	71	25 (4.5)	46 (19.7)
30-40	211	165 (42.3)	46 (21.5)	239	191 (34.6)	48 (20.6)
40-50	163	108 (27.7)	55 (25.7)	245	184 (33.3)	61 (26.2)
50-60	94	51 (13.1)	43 (20.1)	159	110 (19.9)	49 (21.0)
>60	62	21 (5.4)	41 (19.2)	71	42 (7.6)	29 (12.4)

Aff Affected, *Unaff* Unaffected, *SD* Standard deviation.

Table 2 | Association of PRSs with BC risk in BRCA carriers

PRS	*BRCA1* PV carriers (390 affected; 214 unaffected)		*BRCA2* PV carriers (552 affected; 233 unaffected)	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Asian PRS				
PRS_{333}	1.15 (0.97–1.36)	0.1046	1.04 (0.88–1.22)	0.6755
PRS_{GWS}	1.47 (1.10–1.95)	**0.0089**	1.43 (1.04–1.95)	**0.0255**
European PRS				
$PRS_{OVERALL}$	1.16 (0.98–1.37)	0.0761	1.09 (0.92–1.28)	0.3343
PRS_{ER+}	1.16 (0.98–1.38)	0.0862	1.10 (0.92–1.30)	0.3042
PRS_{ER-}	1.12 (0.95–1.32)	0.1905	1.07 (0.89–1.29)	0.4738

Analysis was conducted using weighted Cox regression, with the weights estimated based on the average breast cancer incidence among BRCA carriers in four countries. *Aff* Affected, *Unaff* Unaffected.

Table 3 | Proportion of samples in percentile categories of PRS_{GW} and their associations with breast cancer risk

Percentile	*BRCA1* PV carrier				*BRCA2* PV carriers			
	Unaff.	Aff.	Estimated HR (95% CI)	Predicted HR	Unaff.	Aff.	Estimated HR (95% CI)	Predicted HR
0-20	44	57	0.89 (0.52–1.52)	0.59	48	62	0.44 (0.24–0.80)	0.61
20-40	43	42	0.61 (0.34–1.07)	0.82	47	91	0.91 (0.53–1.59)	0.83
40-60	43	72	1	1	47	109	1	1
60-80	43	102	1.57 (0.96–2.55)	1.23	47	136	1.22 (0.73–2.04)	1.21
80-100	44	121	1.57 (0.99–2.49)	1.23	47	155	1.09 (0.67–1.80)	1.67

Aff Affected, *Unaff* Unaffected.

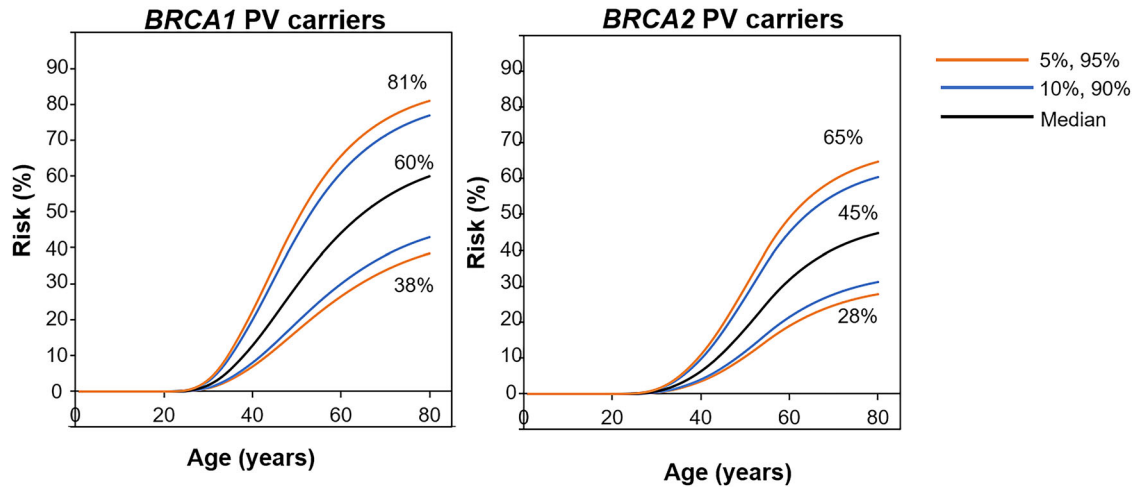

Fig. 1 | Age-specific absolute cumulative breast cancer risks for PV carriers by PRS percentiles according to PRS_{GW}. a *BRCA1* PV carriers and **(b)** *BRCA2* PV carriers.

carriers at the 95th percentile of the PRS distribution had a 30% breast cancer risk by age 50 years and 65% by age 80 years.

Discussion

In this study, we evaluated the association of PRS, previously validated in the Asian general population, with the risk of breast cancer among carriers of *BRCA1* and *BRCA2* PVs of Asian ancestry. While all estimated HRs were above one 1 for all PRS, the association was statistically significant only for the PRS_{GW}, constructed using approximately 1 million variants. The magnitude of the association was markedly higher than for the other PRS in both *BRCA1* (1.47 versus 1.12–1.16) and *BRCA2* (1.43 versus 1.04–1.10) PV carriers.

This is qualitatively consistent with our previous observations in the general population, which showed that PRS_{GW} (HR = 1.62, 95% CI:1.46–1.80) outperformed PRS_{333} (HR=1.53, 95%CI:1.37–1.71) and $PRS_{OVERALL}$ (HR = 1.46, 95%CI:1.34–1.60) in prospective cohorts[10], although the difference was much less marked. PRS_{GW} was developed through integrating GWAS summary statistics from multiple populations and leveraging linkage disequilibrium diversity across discovery samples[11]. This enables more accurate effect size estimation and hence improves the predictive accuracy of PRS in the target population.

We found that the estimated effect sizes for all of the PRS on cancer risks in *BRCA1* and *BRCA2* PV carriers were lower than those previously observed in the general population: for PRS_{GW}, the corresponding HR in Asian prospective cohorts was 1.62 (95%CI:1.46-1.80). Again, attenuation is qualitatively consistent with what was observed in European populations (e.g., for the 313SNV PRS, the HR was estimated to be 1.61 in the general population compared to 1.20 and 1.31 in *BRCA1* and *BRCA2* PV carriers[4,8]).

In the European studies, the PRS adapted for ER-negative breast cancer (PRS_{ER-}) was shown to be more predictive than $PRS_{OVERALL}$ for breast

cancer risk in *BRCA1* PV carriers, consistent with the known strong association of *BRCA1* PVs with ER-negative (specifically triple negative) breast cancer, while $PRS_{OVERALL}$ was more predictive for *BRCA2* PVs. $PRS_{OVERALL}$ was clearly weaker in *BRCA1* than *BRCA2* PVs. This difference was not apparent in this study, possibly due to chance, given the wide confidence limits.

Previous research by Kuchenbäcker et al.[3], indicating improved performance of an 88-SNV PRS in the European population after incorporating *BRCA*-specific SNVs identified from *BRCA1* and *BRCA2* specific genome-wide association studies (GWAS) compared to 77-SNV PRS derived from the general population. This suggests including variants that are associated with cancer risk in *BRCA1* and *BRCA2* PV carriers might potentially further improve the predictive accuracy of PRS. However, SNVs for Asian *BRCA* PV carriers remain elusive as current GWAS in *BRCA* PV carriers lack representation from Asian populations.

We showed that PRS_{GW} can achieve a useful level of risk stratification in Asian *BRCA1* and *BRCA2* PV carriers, where the cumulative risk was substantially lower for carriers in the lowest PRS percentile compared to the highest PRS percentile (Fig. 1). A previous study has shown that the absolute breast cancer risk of Asian PV carriers varies depending on the underlying population-specific cancer incidence[6]. Asian carriers residing in countries with significantly lower population cancer incidences are expected to have markedly lower absolute cancer risks compared to European ancestry carriers. While risk stratification by PRS may not alter screening recommendations, it can refine risk assessment. For instance, carriers identified as having lower risk may consider delaying prophylactic surgeries, such as mastectomy or oophorectomy, thus balancing the benefits and potential harms of such interventions. Implementation of PRS comprising such an expansive SNV set can be difficult in practice. However, given the significant findings, PRS_{GW} can be an alternative until larger GWAS of Asian ancestry *BRCA1* and *BRCA2* PV carriers become available for the development of *BRCA*-specific PRS.

One limitation of our study is that although this is the largest available dataset for Asian *BRCA1* and *BRCA2* PV carriers, our study may lack the power to detect associations with PRS of marginal magnitude. Moreover, the confidence limits associated with the HR estimates were wide. Sensitivity analyses utilizing weights derived from country-specific cancer incidence rates yielded generally comparable HRs to those derived from average cancer incidence rates. However, the statistical significance was reduced in the sensitivity analysis, particularly among *BRCA1* PV carriers. This attenuation may be due to additional heterogeneity introduced when applying country-specific incidence rates to stratified age groups, particularly where sample sizes within certain age-country strata were small (Supplementary Table S4). These findings highlight the challenges in achieving robust statistical power in subgroup analyses and underscore the need for larger, well-powered studies in diverse populations.

In summary, the results demonstrate the potential utility of PRS_{GW} in predicting the risk of breast cancer for Asian carriers of both *BRCA1* and *BRCA2* PVs. Incorporating this polygenic risk score into risk prediction models for PV carriers, alongside other risk modifiers, may be crucial for refining population-specific cancer risk assessments, especially for Asian carriers with a lower risk of breast cancer.

Methods

Study population

Eligible study subjects included in the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA) were self-reported Asian female carriers of a pathogenic or likely pathogenic variant (PV) in either *BRCA1* or *BRCA2* who were age 18 years or older. The germline mutations were classified as pathogenic or likely pathogenic if they resulted in a truncated protein or have been previously reported as disease-associated by ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) or ENIGMA BRCA1/2 expert panel guidelines (https://enigmaconsortium.org/) based on ACMG/AMP Guidelines. Carriers with variants of uncertain significance were excluded. Carriers were recruited from seven study centres in four countries, as part of either population or hospital-based case-control studies, or through genetics clinics (Supplementary Table S1). All research reported here was performed in accordance with the Declaration of Helsinki and each of the study centres recruited carriers under protocols approved by local ethics review boards. The Malaysian Breast Cancer Genetic Study (MyBrCa) was approved by the Independent Ethics Committee, Ramsay Sime Darby Health Care (reference no: 201109.4 and 201208.1), and the Medical Ethics Committee, University Malaya Medical Centre (reference no: 842.9). SGBCC was approved by the National Healthcare Group Institutional Review Board (NHG DSRB Ref: 2009/00501, approval date 16 December 2009) and the SingHealth Duke-NUS Institutional Review Board (CIRB Ref: 2019/2246, approval date 29 October 2010). Each study listed was approved by the local institutional ethics committees and review boards. Written informed consent was obtained from all subjects. Subjects without genotype data were excluded from the analyses, leaving 604 *BRCA1* (390 affected with breast cancer, 96 with ovarian cancer, 118 unaffected with either cancer) and 785 *BRCA2* (552 affected with breast cancer, 46 with ovarian cancer, 187 unaffected) PV carriers in this study. Blood samples were genotyped with the iCOGS array or Oncoarray, which provides genome-wide genotyping[12,13]. Standard quality control processes applied to the genotype data have been described in detail elsewhere[14,15]: these, which included assessment of the SNV call rate, allele frequency, genotyping intensity clustering metrics, Hardy-Weinberg equilibrium and SNV concordance in duplicate samples. Genotypes for variants not on the arrays were estimated using two-stage imputation, using SHAPEIT and IMPUTE2, with the 1000 Genomes Project (Phase 3) samples as the reference panel.

Polygenic Risk Score

PRS were computed using the standard formula:

$$PRS = \beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_k x_k + \ldots + \beta_n x_n \quad (1)$$

where x_k is the dosage of risk allele (0-2) for SNV k and β_k is the corresponding log odds ratio for SNV k.

The list of SNVs and their corresponding log odds ratios is in accordance with those reported in previous publications. $PRS_{OVERALL}$ was based on the 313 SNV PRS developed by Mavaddat et al. For these analyses, the PRS was restricted to the 287 SNVs with imputation accuracy >0.9 in the Asian studies (that is, the original weights were used for the 287 SNVs, but weights for the remaining 26 SNVs were set to zero)[9]. PRS_{ER+} and PRS_{ER-} are modified versions of $PRS_{OVERALL}$ in which the weights from Mavaddat *et* al optimised for the prediction of ER+ and ER- negative, were used. The trans-ancestry PRS, PRS_{333}, was a weighted average of the European-based $PRS_{OVERALL}$ and 46 SNV PRS derived from GWAS in Asian populations, as given in Ho et al.[10]. Thus, PRS_{333} was derived using:

$$PRS_{333} = \alpha_1 PRS_{ASN} + \alpha_2 PRS_{OVERALL} + \alpha_0, \quad (2)$$

where $\alpha_1 = 0.14893$, $\alpha_2 = 0.35354$, and $\alpha_0 = -0.05224$, and PRS_{ASN} was a 46 SNV PRS. The final PRS, PRS_{GW}, was derived as a weighted average of European and Asian-specific PRS, generated using a Bayesian polygenic prediction model in PRS-CSx, thus:

$$PRS_{GW} = \alpha_1 PRS_{GW\_ASN} + \alpha_2 PRS_{GW\_EUR} + \alpha_0, \quad (3)$$

where $\alpha_1 = 0.16856$, $\alpha_2 = 0.38484$, and $\alpha_0 = 0.54881$. Lists of SNVs and the corresponding weights as describe in the original articles.

To facilitate a direct comparison of the performance of each PRS, we standardized the PRS to the standard deviation (SD) of the PRS in the validation set of control subjects previously reported[9,10].

Statistical analysis

The association between each PRS and the incidence of breast cancer was evaluated in a survival analysis framework. Individuals were considered at risk from birth and censored at the age of the first breast or ovarian cancer diagnosis, age at bilateral prophylactic mastectomy, or the age at last follow-up. There were two women in the study with censoring age > 80 (both with age of last follow-up at age 81). PV carriers censored at ovarian cancer diagnosis were considered unaffected for the breast cancer analysis. To account for the oversampling of affected *BRCA1* and *BRCA2* PV carriers, the association of each PRS with breast cancer risk was analysed using a weighted cohort Cox regression with time to breast cancer diagnosis as the outcome[16]. This method involves assigning different weights to affected and unaffected individuals, which are age- and gene-specific, so that the weighted observed incidence rate aligned with externally derived incidence rates for carriers. The country-specific breast cancer incidence rates for *BRCA1* and *BRCA2* PV carriers were estimated using country-specific population breast cancer incidence, the reported log relative risks and the method described in Ho et al.[6], where the log relative risks were assumed to be the same across all countries. The weights for non-random sampling adjustment were calculated based on the average breast cancer incidence rates in *BRCA1* or *BRCA2* PV carriers across all countries. The estimated *BRCA1* and *BRCA2* PV carrier breast cancer incidence rates and the corresponding weights are provided in Supplementary Table S5 and Supplementary Table S6, respectively.

PRS was treated as either a continuous or a categorical variable in the model. The first 4 ancestry principal components (PCs) and birth cohort (in decades) were included as covariates. The robust variance approach was used to account for related individuals in the study by clustering on family membership. All models were fitted separately in *BRCA1* and *BRCA2* PV carriers. When used as a categorical predictor, the PRS was grouped into quintiles based on the PRS distribution in unaffected PV carriers. The middle group (40–60%) was used as the reference category. The observed HRs by PRS percentiles were compared with the theoretical HR predictions under a multiplicative polygenic model of inheritance[17]. The weighted cohort analysis was carried out in R "survival" library command coxph(-model,robust = TRUE,weights = w) where w represents the age-specific weights.

The age-specific absolute risks of developing breast cancer in each PRS percentile were calculated using the following formula described in Barnes et al.[4]:

$$\mathrm{AR_g}(t) = \sum_{u=0}^{t} \lambda_g(u) \cdot \mathrm{S_g}(u) \quad (4)$$

where $\lambda_g(u) = \lambda_0(u)\exp(\beta_g)$ is the estimated breast cancer incidence associated with PRS at age u, with $\lambda_0(u)$ representing the baseline incidence and β_g the corresponding log hazard ratio of association with breast cancer risk for PV carriers in PRS category g relative to the reference category. Here, $S_g(u)$ is the probability of being breast cancer free at age u. The PRS-specific breast cancer incidences, $\lambda_g(u)$, were calculated iteratively by assuming that the average age-specific breast cancer incidence over all PRS percentiles agreed with the estimated average *BRCA1* or *BRCA2* PV carrier breast cancer incidence.

All statistical analyses were conducted using R v.3.6.3.

Data availability

CIMBA data is available on request. To receive access to the data, a concept form must be submitted, which will then be reviewed by the CIMBA Data Access Coordination Committee (DACC). Concept forms and the process of submitting data access requests can be found at: https://www.ccge.medschl.cam.ac.uk/consortium-investigators-modifiers-brca12-cimba/data-data-access.

Code availability

The code for the statistical analysis performed in R v.3.6.3, using the R package survival and rms, and PRS was compute using PLINK 2.0, can be shared with interested readers upon request via email to the corresponding author.

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Competing interests

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Additional information

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