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Development, testing and comparison of novel lifestyle-based prediction models for risk of coronary heart disease

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Prediction of coronary heart disease (CHD) risk through standard equations relying on laboratory-based clinical markers has proven challenging and needs advancement. This study aims to derive and cross-validate novel CHD-risk prediction models based on lifestyle behaviours including wearables and polygenic risk scores (PRS), with comparison to the established Pooled Cohort Equations (PCE) and Systematic COronary Risk Evaluation 2 (SCORE2). This study included 291,151 white British individuals of UK Biobank. Cox regression was applied to derive Lifestyle-Based Model (LBM) for CHD-risk prediction incorporating age, sex, body mass index, dietary intake score (0–3; derived from self-reported food types), smoking status, and physical activity (wearable-device-derived Euclidean Norm Minus One). Weighted PRS for CHD was calculated based on 300 genetic variants. Over a median 13.8-year follow-up, 13,063 CHD incidence cases were ascertained. The C-index (indicative of discrimination) of the LBM, PCE and SCORE2 was 0.713 (95% Confidence Interval [CI]: 0.703–0.722), 0.714 (95% CI: 0.705–0.724) and 0.709 (95% CI: 0.700-0.719). Adding PRS to LBM, PCE and SCORE2 increased the C-index to 0.733 (95% CI: 0.724–0.742), 0.726 (95% CI: 0.716–0.735) and 0.721 (95% CI: 0.711–0.730). The LBM with and without PRS both demonstrated good calibration, demonstrating by p-values of 0.997 and 0.999. The addition of PRS to LBM marginally improved calibration, with the slope increasing from 0.981 to 0.983. Integrating PRS rendered a positive categorical net reclassification improvement (cut-off point: 7.5%) of 4.30% for LBM. The non-laboratory-based LBM, integrating wearable-based and anthropometric data, demonstrated moderate cardiovascular risk prediction accuracy, though external validations remain to be explored.

Keywords Physical activity, Polygenic risk score, Coronary heart disease, UK biobank, Risk prediction modelling

Abbreviations

CHD	coronary heart disease
CVD	cardiovascular disease
PRS	polygenic risk score
LBM	Lifestyle-Based Model
LBM + PRS	Lifestyle-Based Model plus polygenic risk score
PCE	Pooled Cohort Equations
PCE + PRS	Pooled Cohort Equations plus polygenic risk score
SCORE2	Systematic COronary Risk Evaluation 2
SCORE2 + PRS	Systematic COronary Risk Evaluation 2 plus polygenic risk score
GWAS	Genome-Wide Association Studies
SNPs	single-nucleotide polymorphisms

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HR	hazard ratio
CI	confidence interval
ENMO	Euclidean Norm Minus One
BMI	body mass index
GND	Greenwood-Nam-D'Agostino
NRI	net reclassification improvement
IDI	integrated discrimination index

Coronary heart disease (CHD), the most prevalent type of cardiovascular disease (CVD), accounts for approximately 33.3% of all-cause mortality and 49.2% of cardiovascular mortality globally[1]. The development of CHD is multi-factorial as it is caused by both genetic and non-genetic environmental factors[2–4]. Evidence indicates that genetic predispositions to CHD account for up to 50% of CVD risk,[5] and CHD can be prevented through adherence to a healthy lifestyle, including regular participation in physical activity, a healthy diet, no smoking, and maintaining a healthy weight[4,6,7].

Accurate assessment of coronary heart disease (CHD) risk is essential for primary prevention as it informs clinical decisions regarding preventive interventions including lifestyle modification and pharmacotherapy[8]. As such, the current clinical guidelines for the prevention of cardiovascular events recommend estimation and provision of the 10-year absolute risk of CHD through the use of risk assessment models, such as the established Pooled Cohort Equations (PCE) and Systematic COronary Risk Evaluation 2 (SCORE2) widely used in the clinical settings[8–11]. However, evidence for the predictive accuracy of the PCE and SCORE2 remains equivocal[12–14]. Notably, the inclusion of multiple conventional laboratory-based clinical risk markers (e.g., total/high-density lipoprotein cholesterol, systolic blood pressure) as predictors in the PCE and SCORE2 makes the equations less practical for use by general populations and in the community/household settings where the collection of such information is not feasible. Another limitation of the PCE and SCORE2 is the lack of incorporation of prominent lifestyle behaviours, which are key markers of cardiovascular risk[9]. Currently, there is no CHD risk prediction model that integrates multiple lifestyle predictors (e.g., physical activity, diet, smoking) particularly wearable indicators. The purpose of this study was, therefore, to derive and cross-validate lifestyle-based prediction models for CHD risk by integrating polygenic risk scores (PRS) and multiple lifestyle predictors including wearable-device-measured physical activity, and evaluate the predictive performance in comparison to the PCE and SCORE2 approach using large-scale national cohort data.

Methods

Participants and study design

This study used data from UK Biobank, which is an ongoing prospective cohort study of over half a million participants aged 40–69 years at recruitment (5.5% response rate out of around 9,000,000 eligible individuals)[15]. The study protocol of the UK Biobank, detailed in eText 1, was approved by the North West Multicentre Research Ethics Committee (11/NW/0382). The conduct of the present study was approved by the Institutional Review Board of The University of Hong Kong / Hospital Authority Hong Kong West Cluster (UW 21–542). All measurements and experiments were performed in accordance with relevant guidelines and regulations, and all participants provided written informed consent prior to participation[15].

The present study included 291,151 individuals who met the following inclusion criteria: (1) having self-reported as European descendants ('white British') with verification by principal component analysis of genetic ancestry, (2) having consistent self-reported and inferred gender information, (3) having no prevalence of cardiovascular events at baseline (i.e., CHD and stroke; based on hospital admission, deaths registries and self-report data), and (4) having no missing values for any predictors and PRS (eFigure 1).

Polygenic risk score (PRS)

In the UK Biobank study, genotyping of all participants was carried out with the UK Biobank Axiom Array and UK BiLEVE Axiom Array, with imputation to a haplotype reference panel of the Haplotype Reference Consortium combined with UK10K[16]. Specifically, the calculation of weighted PRS was based on 300 Single-Nucleotide Polymorphisms (SNPs) known to be associated with the risk of CHD, consisting of genome-wide significant and non-significant SNPs uncorrelated with each other at a false discovery rate of 5% (eTable 1), as applied in a previous study by Ntalla et al.[3] Weighted PRS for CHD risk was then derived by summing the products of the number of risk-increasing alleles at each of the loci and the corresponding effect size identified from the literature[2,3].

Derivation of the Lifestyle-Based Model (LBM)

The LBM was developed using the following variables as predictors, based on the established associations with the risk of CHD:[4] age, sex, body mass index (BMI), dietary intake score (0–3; generated based on self-reported food categories), smoking status (current, previous, never), and physical activity (wrist-worn wearable-device-derived Euclidean Norm Minus One; ENMO, a composite value of 3 axes' acceleration values).

Information on diet and smoking status was collected through the self-reported touch-screen questionnaire. A dietary intake score (ranging from 0 to 3) was constructed based on the guidelines from the AHA,[17] following an established procedure[18]. Both calibrated ENMO and raw ENMO were used as indicators of physical activity. Information on the generation of dietary intake scores and physical activity variables can be found in eText 2 and eText 3[17,18].

Pooled Cohort Equations (PCE) and Systematic COronary Risk Evaluation 2 (SCORE2)

Following the recommended procedures,[12,19] we recalibrated the PCE and SCORE2 in order to match the PCE and SCORE2 predictors to the variables of the UK Biobank database incorporating information on age, sex, smoking status (yes or no), total and high-density lipoprotein cholesterol (mmol/l), blood pressure (mmHg; treated with medications or untreated), and diabetes (yes or no). We re-estimated the rescaling weights obtained from regressing the predicted risk against observed risk using the original PCE published in 2013 and SCORE2 formula for low risk region (the United Kingdom)[10]. Detailed information on the definition and quantification of PCE and SCORE2 risk predictors is provided in eTable 2.

Incidence of CHD

CHD incidence was ascertained through the linkage of UK Biobank participants' measured data with their hospital admission records and death registry[15]. Codes of International Classification of Diseases (ICD) and operative procedures were used to classify CHD events (ICD-9: 410, 411,412.X, ICD-10: I21, I22, I23, I24, I25.2, OPCS: K40 - K46, K49, K50.1, K50.2, K50.4). Incident CHD was defined as the first observation of CHD events that occurred until 9th December 2022 for individuals in England and Wales and 19th December 2022 for individuals in Scotland.

Statistical analyses

The full data sample was randomly split into 5 sub-groups with an approximately equal number of individuals allocated per group (See Fig. 1) for model development and cross-validation of LBM and LBM + PRS. To develop the LBM, we fit Cox proportional hazard models incorporating age, sex, BMI, dietary intake score, smoking status, and physical activity. Following the established methodology for PCE model development,[10] interactions

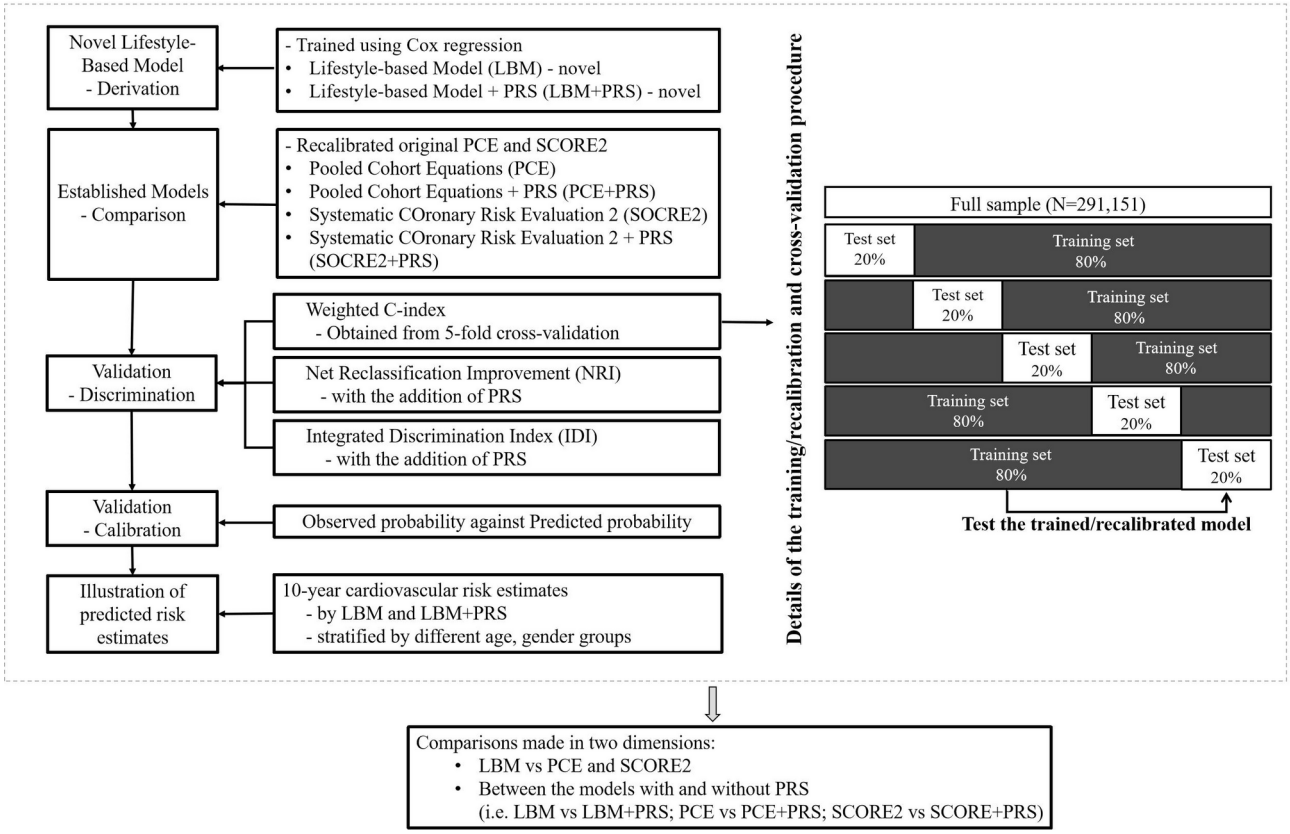


Fig. 1. Study design, model derivation, and model validation process. Notes: LBM: using age, sex, body mass index (BMI), dietary intake score, smoking status (current, previous, never), and physical activity (mg). LBM + PRS: adding polygenic risk scores to the LBM. PCE: using age, sex, smoking status (yes or no), total and high-density lipoprotein cholesterol (mmol/l), treated or untreated systolic blood pressure (mmHg), and diabetes (yes or no). PCE + PRS: adding polygenic risk scores to the PCE. SCORE2: using age, sex, smoking status (yes or no), total and high-density lipoprotein cholesterol (mmol/l), systolic blood pressure (mmHg), and diabetes (yes or no). SCORE2 + PRS: adding polygenic risk scores to the SCORE2. Abbreviations: CHD = coronary heart disease; CI = confidence interval; IDI = Integrated Discrimination Index; LBM = Lifestyle-Based Model; LBM + PRS = Lifestyle-Based Model plus polygenic risk score; NRI = Net Reclassification Improvement; PCE = Pooled Cohort Equations; PCE + PRS = Pooled Cohort Equations plus polygenic risk score; PRS = polygenic risk score; SCORE2 = Systematic COronary Risk Evaluation 2; SCORE2 + PRS = Systematic COronary Risk Evaluation 2 plus polygenic risk score.

of age with each lifestyle-based predictor were tested, and retained as predictors in the model if the p-value was less than 0.01; or the p-value was between 0.01 and 0.05, with a continuous net reclassification improvement (NRI) for non-events ≥ 15% or a statistically significant integrated discrimination index (IDI) in the full sample.

For cross-validation of prediction models (LBM, PCE, SCORE2, LBM+PRS, PCE+PRS and SCORE+PRS), a total of 5 iterations of training/cross-validation were performed, with each 20% sub-group used as a cross-validation set and the remaining 80% subset (i.e., four 20% sub-groups) as a training set in each iteration[20]. Cox regression was fit to estimate the C-index (ranging from 0.5 for no discrimination to 1.0 for perfect discrimination, on average) along with 95% confidence interval (CI) values for each model across the 5 iterations[21] We then weighted each of the 5 C-index values relative to the corresponding number of CHD incidence cases to obtain the weighted average C-index. A paired t-test was performed to evaluate the changes in the C-index between the prediction models with and without the inclusion of the PRS.

To further examine the added value of PRS to the LBM and established algorithms, we evaluated the risk reclassification ability by calculating the continuous NRI (calculated as the sum of "NRI+" [event NRI] and "NRI-" [non-event NRI]), categorical NRI (according to the threshold of 7.5% for LBM and PCE and 10% for SCORE2), and IDI (calculated based on the sum of the integrated sensitivity and integrated specificity, indicative of improvements in the slopes of the discrimination curves) as additional parameters of discrimination[22].

To examine the calibration of the LBM and established prediction models, calibration plots were created by plotting the mean observed Kaplan-Meier estimates (observed probability) against the mean predicted probability within each decile of the predicted probabilities from each model. We also calculated the corresponding calibration slopes (with a "slope value = 1" indicating perfect calibration, on average), and Greenwood-Nam-D'Agostino (GND) P-values[23].

To demonstrate how incidence CHD rates vary by 10-year absolute CHD risk estimates predicted by the six models (LBM, PCE, SCORE2, LBM + PRS, PCE+ PRS and SCORE2 + PRS), we estimated cumulative CHD incidence rates for four risk reclassification groups defined according to 10-year CHD risk estimates, applying the cut-off point of 7.5% for PCE and LBM; and 10% for SCORE2.

A total of 3 sets of sensitivity analyses were performed with details provided in eText 4. Statistical analyses were performed using Stata/MP Version 17.0 (StataCorp LP, College Station, TX) and R (Version 4.4.3).

Results

Participants' characteristics at baseline are presented in eTable 3. Of 291,151 participants, a total of 13,063 CHD cases (3949, cases in women and 9,114 cases in men) were observed over a 13.8-year median follow-up (interquartile range: 13.1–14.4 years). Lifestyle predictors with which age had evidence of interaction included BMI, smoking status and physical activity, all of which were retained in the LBM and LBM + PRS models. The predictive algorithms for estimating 10-year CHD risk using LBM and LBM + PRS models are presented in eTable 4. The calculation of 10-year CHD risk follows the equation: $1\text{-}S_{10}^{e^{(IndX'B-MeanX'B)}}$, where S10 represents the baseline survival rate at 10 years, *IndX'B* denotes the sum of individual risk factor values multiplied by their respective coefficients, and *MeanX'B* represents the population mean of these coefficient-weighted risk factors. The sex-specific recalibration coefficients of the PCE and SCORE2 are shown in eTable 5.

Figure 2 presents the discrimination of the LBM as opposed to the established PCE and SCORE2 as identified through the 5-fold cross-validation. The weighted C-index of the LBM, PCE and SCORE2 was 0.713 (95% CI, 0.703–0.722), 0.714 (95% CI, 0.705–0.724) and 0.709 (95% CI: 0.700-0.719), respectively. When additionally incorporating PRS, there was an improvement in the discriminant performance of both models: C-index values were increased to 0.733 (95% CI, 0.724–0.742) for the LBM + PRS, 0.726 (95% CI, 0.716–0.735) for the PCE + PRS and 0.721 (95% CI, 0.711, 0.730) for the SCORE2 + PRS. The addition of PRS resulted in statistically significant improvements in the C-index, as demonstrated by paired t-test p-values of 0.0002, 0.0034 and 0.0038 for LBM + PRS, PCE + PRS and SCORE2 + PRS, indicating enhanced discrimination. C-index values in each of the 5-fold iterations are presented in eTable 6.

Figure 3 displays the agreement between the observed Kaplan-Meier estimates and predicted estimates of 10-year absolute CHD risk from the six models in the form of calibration plots. LBM, LBM + PRS, PCE and SCORE2 (but not PCE + PRS and SCORE2 + PRS) passed the GND test with the P-value > 0.05, indicating that there was no evidence of difference between the observed risk and predicted risk, on average. The slope of the LBM was 0.981, reflecting a stronger calibration of the LBM prediction, compared with the PCE (slope: 0.954) and SCORE2 (slope: 0.974), with a minimal overestimate of CHD risk, on average. The addition of PRS to the LBM further minimised the difference between the predicted and observed risk with a larger P-value (0.999) and a slope (0.983) closer to 1, albeit a slight overestimation.

Changes in risk reclassification when additionally incorporating PRS are shown in Table 1. The addition of PRS resulted in positive overall NRIs in LBM, PCE and SCORE2 models, which is in line with the pattern of change in the C-index. The overall continuous NRI was 29.9% (15.3% for cases and 14.7% for non-cases) for the LBM + PRS, 28.4% (14.3% for cases and 14.0% for non-cases) for the PCE + PRS, and 28.3% (14.3% for cases and 13.9% for non-cases) for SCORE2 + PRS. The direction of change in the overall categorical NRI (cut-off point: 7.5%/10%) and IDI is significant and consistent with the direction of change in the continuous NRI for the LBM + PRS, PCE + PRS and SCORE2 + PRS. The overall categorical NRI for the LBM + PRS was 4.30%, with 4.78% for cases and − 0.49% for non-cases. The categorical NRI for the PCE + PRS and SCORE2 + PRS was 4.29% (5.04% for cases and − 0.75% for non-cases) and 3.09% (3.45% for cases and − 0.39% for non-cases). Proportions of cases and non-cases reclassified according to the 7.5%/10% risk threshold are presented in eTable 7. The IDI for the LBM + PRS, PCE + PRS and SCORE2 + PRS was 0.62%, 0.60% and 0.59%, respectively, which suggests an increment in risk differences between non-cases and cases with the addition of PRS.

Figure 4 shows the cumulative incidence of CHD for risk reclassification groups generated based on 10-year CHD risk estimates from the prediction models. With respect to the LBM and LBM + PRS, the highest

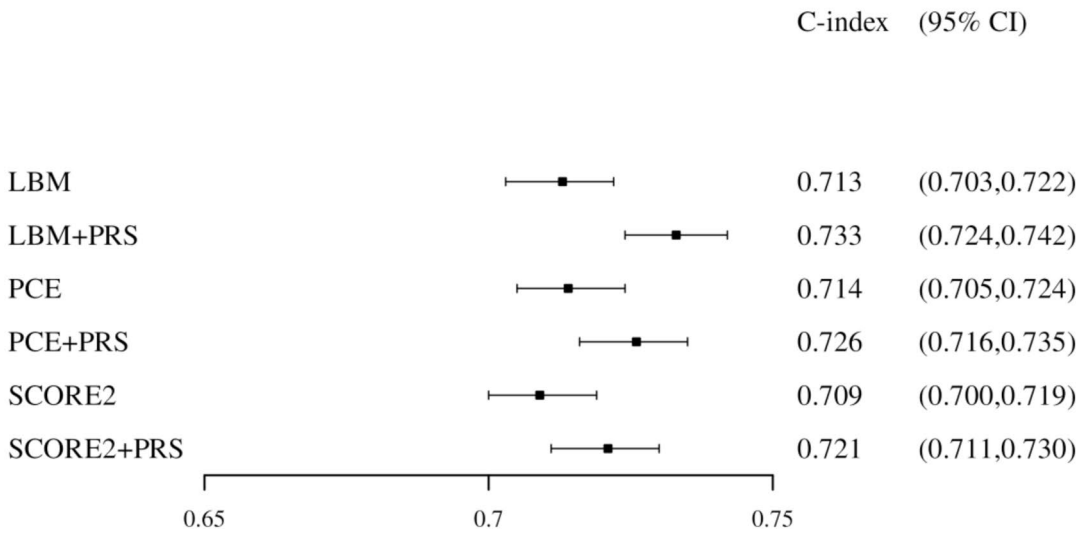


Fig. 2. Discriminant performance (C-index) of prediction models as identified through 5-fold cross-validation. Notes: LBM: using age, sex, body mass index (BMI), dietary intake score, smoking status (current, previous, never), and physical activity (mg). LBM + PRS: adding polygenic risk scores to the LBM. PCE: using age, sex, smoking status (yes or no), total and high-density lipoprotein cholesterol (mmol/l), treated or untreated systolic blood pressure (mmHg), and diabetes (yes or no). PCE + PRS: adding polygenic risk scores to the PCE. SCORE2: using age, sex, smoking status (yes or no), total and high-density lipoprotein cholesterol (mmol/l), systolic blood pressure (mmHg), and diabetes (yes or no). SCORE2 + PRS: adding polygenic risk scores to the SCORE2. Abbreviations: CHD = coronary heart disease; CI = confidence interval; LBM = Lifestyle-Based Model; LBM + PRS = Lifestyle-Based Model plus polygenic risk score; PCE = Pooled Cohort Equations; PCE + PRS = Pooled Cohort Equations plus polygenic risk score; PRS = polygenic risk score; SCORE2 = Systematic COronary Risk Evaluation 2; SCORE2 + PRS = Systematic COronary Risk Evaluation 2 plus polygenic risk score.

cumulative incidence of CHD was observed in the 'shared high risk' category (i.e. 10-year risk estimates ≥ 7.5% by both the LBM and LBM + PRS), followed by 'up-classified' (i.e. 10-year risk estimates ≥ 7.5% by LBM + PRS, but 10-year risk estimates < 7.5% by LBM), 'down-classified' (i.e. 10-year risk estimates < 7.5% by LBM + PRS, but 10-year risk estimates ≥ 7.5% by LBM), and 'shared low risk' (i.e. 10-year risk estimates < 7.5% by both the LBM and LBM + PRS). A similar pattern of cumulative CHD incidence was observed for the PCE + PRS (cut-off point: 7.5%) and SCORE2 + PRS (cut-off point: 10%). As shown in eFigure 3, for each of the six models, cumulative CHD incidence rates were also greater in individuals at high risk (≥ 7.5% or ≥ 10%) than in those at low risk (< 7.5% or < 10%).

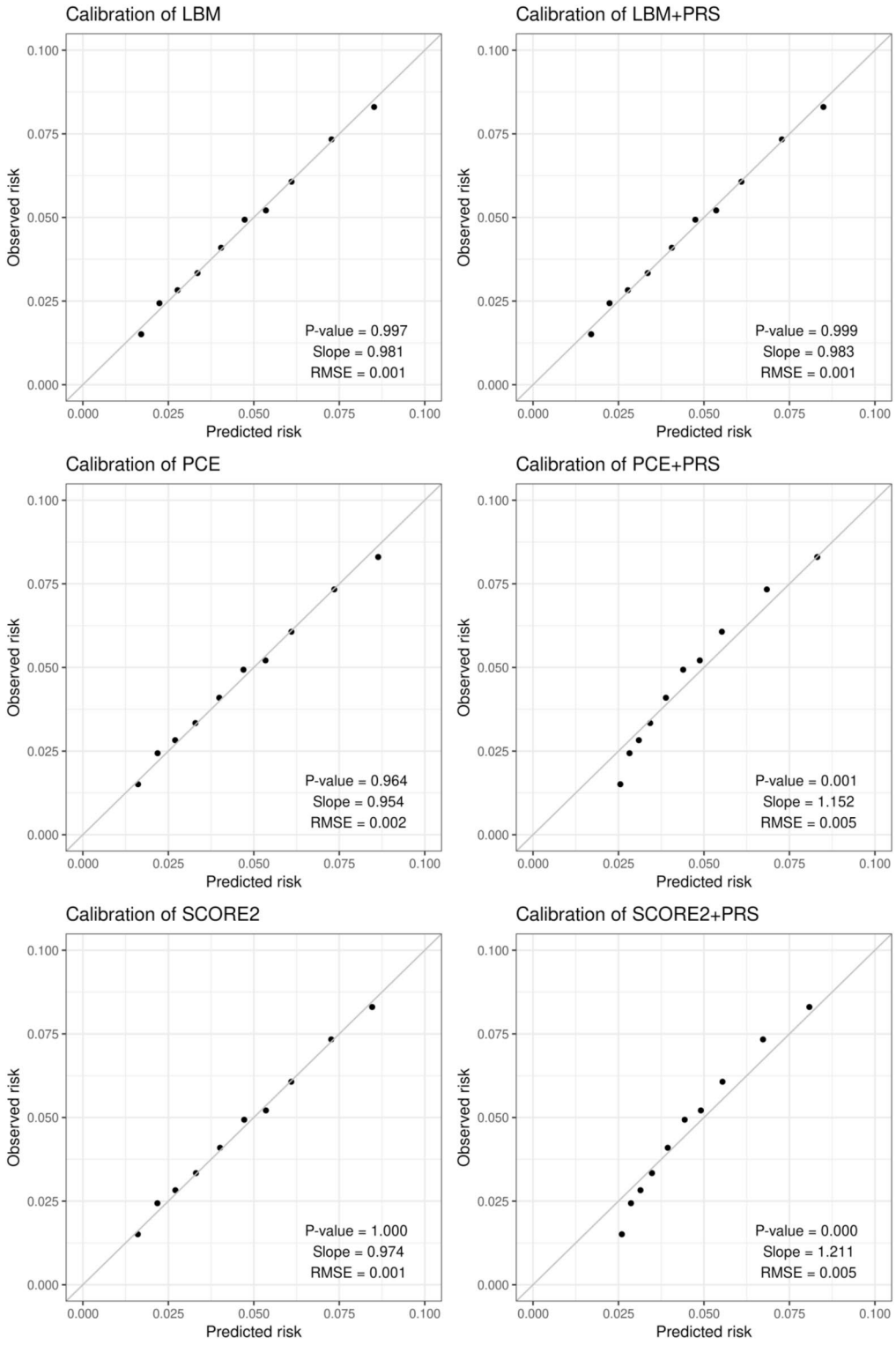
Figure 5 shows the distribution of 10-year CHD risk estimates, derived from LBM and LBM + PRS, varies across age-specific and sex-specific groups. The proportions of individuals expected in each risk category indicate that predicted risks are generally higher in males than in females, and older age groups exhibit greater risk compared to younger ones. Compared to the LBM, the LBM + PRS offers a more nuanced differentiation of individual risk estimates across various gender and age levels.

Results of the sensitivity analyses are presented in eFigures 4–9 and eTables 8–17, showing generally similar patterns of findings as the main analysis. For example, the LBM models demonstrated acceptable predictive accuracy not only in an independent hold-out set, but also in relation to the PCE and SCORE2 models.

Discussion

This is the first study deriving and cross-validating CHD risk prediction models based on lifestyle behaviours including wearable-device-measured physical activity in conjunction with genetic risk markers. The LBMs demonstrated comparable predictive ability compared to the PCE and SCORE2 models. In addition, we found that there was a modest improvement in predictive accuracy after the addition of PRS to LBM.

Using a series of statistical procedures recommended by the guidelines of precise medicine research, we evaluated the predictive performance of the risk prediction models in terms of discriminant ability, risk reclassification and calibration[20–23]. The similar discriminant ability and calibration of the LBM as the PCE and SCORE2 suggest that estimates of CHD risk predicted by the LBM are, in general, comparable to those predicted by the PCE and SCORE2. No previous studies have established CHD prediction models integrating multiple lifestyle predictors, although up to 80–90% of CHD mortality cases may be attributable to lifestyle risk factors[5,24]. The derivation and testing of the LBM, of which risk predictors are non-clinical, easy-to-assess lifestyle indicators along with key demographic variables, offer possibilities of CHD risk prediction performed not only under



clinical settings, but also under non-clinical community settings where routine collection of clinical markers is not feasible. The widespread use of wearable devices coupled with significant advances in wearable technology would allow for more streamlined acquisition and processing of the wearable-device-measured PA parameters included in the LBM. Given that all predictive factors in the LBM are accessible without the need for laboratory testing, this new predictive model will enable individuals to assess their cardiovascular risk conveniently at any time and place. Such approaches hold great potential for facilitating pre-emptive identification of individuals at elevated risk of cardiovascular events, allowing for the prompt implementation of preventive measures including lifestyle modification[25,26]. In this sense, while the use of the PCE and SCORE2 has been formally recommended to use in the clinical setting,[10] the LBM may be used as a feasible stand-alone CHD risk prediction tool in the primary care setting. The LBM framework, as a non-invasive risk assessment tool leveraging wearable data, highlights modifiable lifestyle factors to enable personalized cardiovascular risk evaluation. While the current

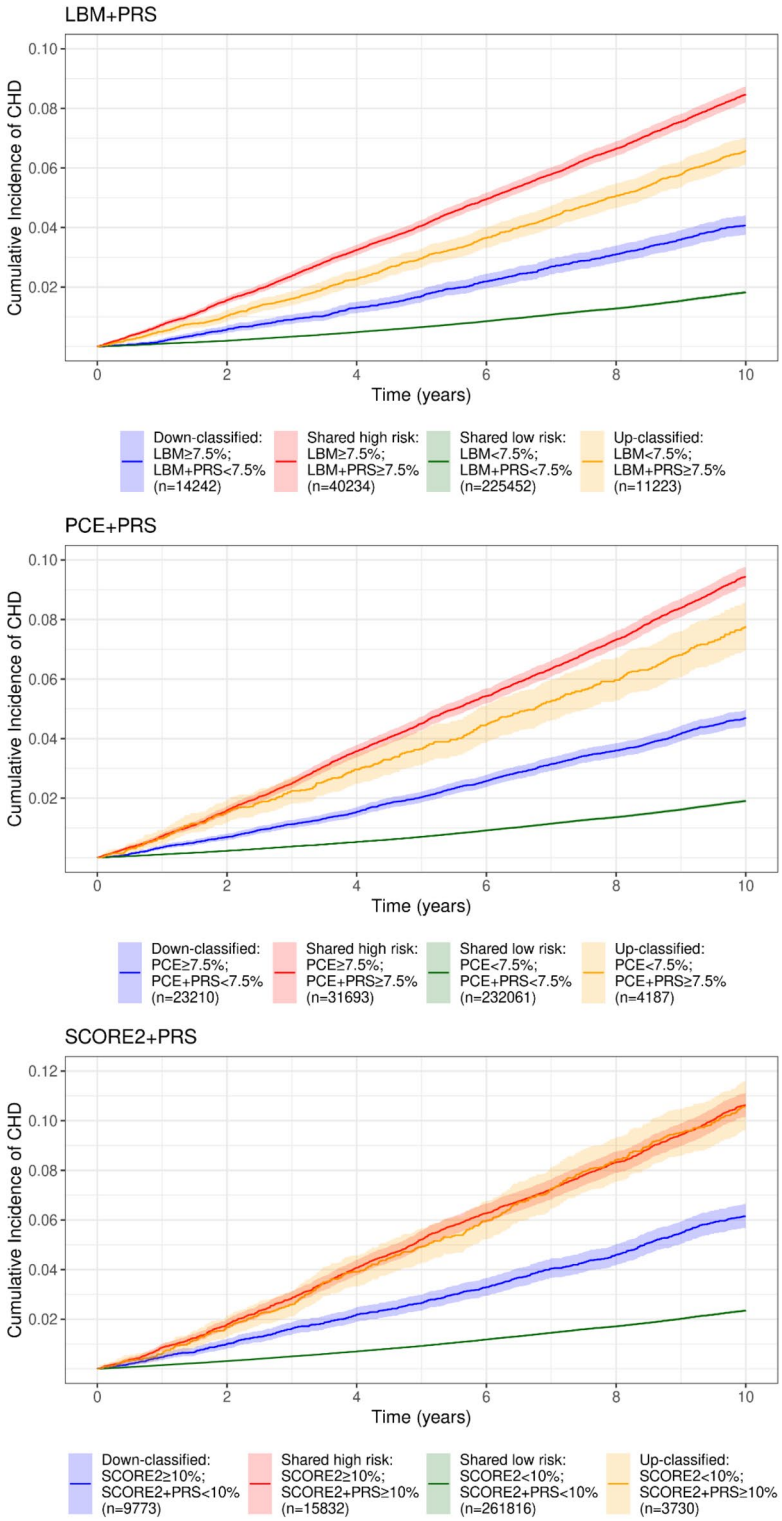
◀**Fig. 3**. Calibration plots and P-values for Greenwood-Nam-D'Agostino (GND) tests across four prediction models. Notes: P-values reported are derived from Greenwood-Nam-D'Agostino tests, which examine the null hypothesis that the observed and predicted probabilities in each group are identical, on average. The slope represents the relationship between the observed and predicted probability, with the slope = 1 suggesting perfect calibration, on average. LBM: using age, sex, body mass index (BMI), dietary intake score, smoking status (current, previous, never), and physical activity (mg). LBM + PRS: adding polygenic risk scores to the LBM. PCE: using age, sex, smoking status (yes or no), total and high-density lipoprotein cholesterol (mmol/l), treated or untreated systolic blood pressure (mmHg), and diabetes (yes or no). PCE + PRS: adding polygenic risk scores to the PCE. SCORE2: using age, sex, smoking status (yes or no), total and high-density lipoprotein cholesterol (mmol/l), systolic blood pressure (mmHg), and diabetes (yes or no). SCORE2 + PRS: adding polygenic risk scores to the SCORE2. Abbreviations: CHD = coronary heart disease; LBM = Lifestyle-Based Model; LBM + PRS = Lifestyle-Based Model plus polygenic risk score; PCE = Pooled Cohort Equations; PCE + PRS = Pooled Cohort Equations plus polygenic risk score; PRS = polygenic risk score; RMSE = Root-mean-square error (the standard deviation of the residuals); SCORE2 = Systematic COronary Risk Evaluation 2; SCORE2 + PRS = Systematic COronary Risk Evaluation 2 plus polygenic risk score.

	LBM + PRS		PCE + PRS		SCORE2 + PRS	
	Estimate	**95%CI**	**Estimate**	**95%CI**	**Estimate**	**95%CI**
Continuous NRI						
Overall NRI	29.9%	(27.9%, 32.1%)	28.4%	(26.4%, 30.5%)	28.3%	(26.2%, 30.4%)
NRI+	15.3%	(13.7%, 17.1%)	14.3%	(12.8%, 16.0%)	14.3%	(12.8%, 16.1%)
NRI-	14.7%	(13.9%, 15.5%)	14.0%	(13.2%, 14.9%)	13.9%	(13.1%, 14.7%)
Categorical NRI (7.5% - LBM) (7.5% - PCE) (10% - SCORE2)						
Overall NRI	4.30%	(3.54%, 5.01%)	4.29%	(3.52%, 4.92%)	3.09%	(2.57%, 3.66%)
NRI+	4.78%	(3.97%, 5.48%)	5.04%	(4.21%, 5.71%)	3.45%	(2.90%, 4.05%)
NRI-	-0.49%	(-0.60%, -0.38%)	-0.75%	(-0.85%, -0.65%)	-0.35%	(-0.42%, -0.29%)
IDI	0.62%	(0.56%, 0.70%)	0.60%	(0.53%, 0.68%)	0.59%	(0.52%, 0.67%)

Table 1. Changes in risk reclassification when additionally including polygenic risk score (PRS) in prediction models. Notes: The formula defining overall NRI, NRI+ and NRI- are shown as follows: Overall NRI = $P_{(up|cases)} - P_{(down|cases)} - P_{(up|non\text{-}cases)} + P_{(down|non\text{-}cases)}$; NRI+ = $P_{(up|cases)} - P_{(down|cases)}$; and NRI- = $P_{(down|non-cases)} - P_{(up|non-cases)}$. "Cases" refer to individuals with the incidence of CHD, and "non-cases" refer to individuals without the incidence of CHD; "up" means that the model with PRS added ranks an individual into a higher risk category than the old model, whereas "down" means that the model with PRS added ranks an individual into a lower risk category. LBM: using age, sex, body mass index (BMI), dietary intake score, smoking status (current, previous, never), and physical activity (mg). LBM + PRS: adding polygenic risk scores to the LBM. PCE: using age, sex, smoking status (yes or no), total and high-density lipoprotein cholesterol (mmol/l), treated or untreated systolic blood pressure (mmHg), and diabetes (yes or no). PCE + PRS: adding polygenic risk scores to the PCE. SCORE2: using age, sex, smoking status (yes or no), total and high-density lipoprotein cholesterol (mmol/l), systolic blood pressure (mmHg), and diabetes (yes or no). SCORE2 + PRS: adding polygenic risk scores to the SCORE2. Abbreviations: CHD = coronary heart disease; CI = confidence interval; IDI = Integrated Discrimination Index; LBM = Lifestyle-Based Model; LBM + PRS = Lifestyle-Based Model; NRI = Net Reclassification Improvement; PCE = Pooled Cohort Equations; PCE + PRS = Pooled Cohort Equations plus polygenic risk score; PRS = polygenic risk score; SCORE2 = Systematic COronary Risk Evaluation; 2SCORE2 + PRS = Systematic COronary Risk Evaluation 2 plus polygenic risk score.

design does not support longitudinal tracking of risk trajectory in response to lifestyle modifications, the model's capacity for self-assessments empower users with actionable feedback on lifestyle impacts. This iterative approach may enhance heightened risk awareness—a crucial precursor to behavioral change—though its long-term influence on lifestyle modifications requires further validation.

Improvements in predictive accuracy when incorporating PRS demonstrate the potential utility of genetic markers in CHD risk prediction[27–30]. Previous studies using UK Biobank data found that adding PRS to the PCE (i.e. PCE + PRS) modestly improved risk reclassification ability[13,29]. While the present study corroborates these findings on improved risk classification and discriminant ability, our results suggest that incorporating PRS into PCE or SCORE2 may not necessarily enhance the calibration. For comparison, we found that adding PRS into CHD risk prediction models based on lifestyle factors could lead to an improvement in not only discrimination but also calibration. Notably, the increment in C-index was generally greater for the LBM than for the PCE and SCORE2 when adding PRS. These phenomena may be explained by the inclusion of clinical markers (e.g. blood pressure, cholesterol) as predictors in the PCE and SCORE2, which are characterised by the



joint influences of environmental and genetic traits, with the latter having shared mechanisms accounted for by genetic susceptibility to CHD (i.e. PRS)[31–33]. Therefore, adding PRS to prediction models based on clinical factors may confer a relatively smaller gain in discriminatory ability, and could, thereby, potentially decrease calibration. Further research is needed to elucidate the extent to which clinical markers are modified by PRS for CHD risk in order to validate the actual value of incorporating PRS into CHD risk prediction relying on standard cardiovascular risk markers. Taken together, the addition of PRS into prediction models incorporating lifestyle indicators or clinical risk markers could be taken into consideration with cautiousness in clinical applications aimed at early identification of individuals at elevated risk of CHD, as well as improved prediction of CHD risk[34,35].

◀**Fig. 4**. Cumulative incidence of coronary heart disease (CHD) for risk reclassification groups defined based on 10-year CHD risk estimates derived from prediction models. Notes: All participants are divided into four risk reclassification groups according to their 10-year risk estimates predicted by models using the cut-off point of 7.5% for LBM and PCE models; and the cut-off point of 10% for SCORE2. For example, the 'shared high risk' category (i.e. 10-year risk estimates ≥ 7.5% by both the LBM and LBM + PRS), followed by 'up-classified' (i.e. 10-year risk estimate ≥ 7.5% by LBM + PRS, while 10-year risk estimates < 7.5% by LBM), 'shared low risk' (i.e. 10-year risk estimates < 7.5% by both the LBM and LBM + PRS) and 'down-classified' (i.e. 10-year risk estimates < 7.5% by LBM + PRS, while 10-year risk estimates ≥ 7.5% by LBM). LBM: using age, sex, body mass index (BMI), dietary intake score, smoking status (current, previous, never), and physical activity (mg). LBM + PRS: adding polygenic risk scores to the LBM. PCE: using age, sex, smoking status (yes or no), total and high-density lipoprotein cholesterol (mmol/l), treated or untreated systolic blood pressure (mmHg), and diabetes (yes or no). PCE + PRS: adding polygenic risk scores to the PCE. SCORE2: using age, sex, smoking status (yes or no), total and high-density lipoprotein cholesterol (mmol/l), systolic blood pressure (mmHg), and diabetes (yes or no). SCORE2 + PRS: adding polygenic risk scores to the SCORE2. Abbreviations: CHD = coronary heart disease; CI = confidence interval; IDI = Integrated Discrimination Index; LBM = Lifestyle-Based Model; LBM + PRS = Lifestyle-Based Model; NRI = Net Reclassification Improvement; PCE = Pooled Cohort Equations; PCE + PRS = Pooled Cohort Equations plus polygenic risk score; PRS = polygenic risk score; SCORE2 = Systematic COronary Risk Evaluation; 2SCORE2 + PRS = Systematic COronary Risk Evaluation 2 plus polygenic risk score.

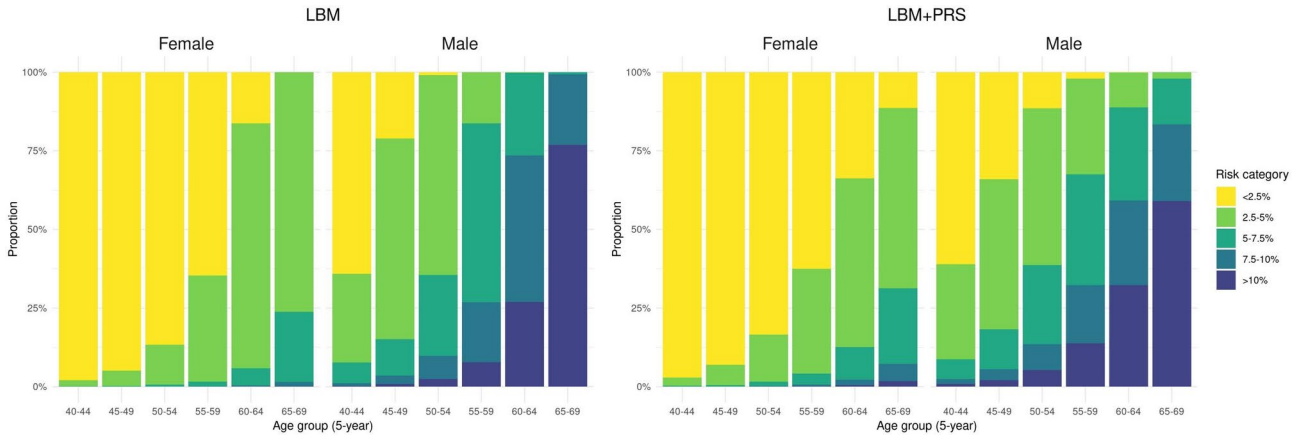


Fig. 5. Estimates of 10-year cardiovascular risk distribution based on Lifestyle-Based Models across various age and sex groups. Notes: The figure reflects the 10-year coronary heart disease risk estimates by LBM and LBM + PRS in sex-specific and age-specific groups. LBM: using age, sex, body mass index (BMI), dietary intake score, smoking status (current, previous, never), and physical activity (mg). LBM + PRS: adding polygenic risk scores to the LBM. Abbreviations: LBM = Lifestyle-Based Model; LBM + PRS = Lifestyle-Based Model; NRI = Net Reclassification Improvement.

Strengths and limitations

The present study has multiple strengths worth noting. First, we employed rigorous statistical procedures to cross-validate the discriminant ability, risk reclassification and calibration of our newly developed prediction model (e.g., LBM), and compared it against an established prediction model (PCE and SCORE2); while many of the previous studies only presented the results of discrimination without calibration, and/or cross-validation[36]. Second, the use of a large-scale cohort dataset (n = 291,151) with a large number of CHD events (n = 13,063) adjudicated over a median 13.8-year follow-up ensured sufficient statistical power in the conduct of training/recalibration and testing of the models. Furthermore, the present study used wearable device data to derive indicators of physical activity[37]. Third, unlike traditional risk models that rely on clinical markers, our model leverages non-invasive, wearable-derived lifestyle indicators, making it more accessible for broader population-level screening and self-assessment.

However, several limitations must be considered when interpreting the findings of the present study. First, the analysis was restricted to individuals of European ancestry from UK Biobank who have more favourable metabolic profiles, compared with the general adult population,[31] which limits the generalisability of our findings. Nevertheless, this study informs future work on the construction of comparable lifestyle-based models for feasible and accurate prediction of cardiovascular risk in individuals of different socio-economic backgrounds, particularly those in developing countries where the burden of CHD is increasingly high with limited healthcare resources[38,39]. Second, while the models included herein were all cross-validated, no external validation was carried out using datasets external to UK Biobank data. Future studies are warranted to examine the external validity of the models developed herein not only in non-UK Biobank samples but also in individuals of different ethnic backgrounds and age ranges. Third, some of the self-reported predictors may have measurement errors,

while the LBM demonstrated acceptable predictive accuracy as compared with the model performance of PCE and SCORE2[37]. Given these limitations, when replicating the LBM in other populations, the recalibration process, as recommended by the working groups of PCE and SCORE2,[8–11] will be essential. Furthermore, we only used data from baseline timepoint in explaining the lifestyle in the analyses. Future studies incorporating larger samples of individuals with repeated measures are warranted to allow for prediction of CHD risk through changes in risk predictors.

Conclusion

The novel LBM and LBM + PRS both have acceptable accuracy for the prediction of first-onset CHD events comparing with PCE and SCORE2. The addition of PRS results in a modest improvement in the predictive accuracy of CHD risk for the LBM, PCE and SCORE2 (except calibration). Our novel models integrating either lifestyle predictors or in combination with genetic traits have great potential to serve as an accurate and feasible CHD-risk prediction method.

Data availability

The dataset supporting the conclusions of this study is available in the UK Biobank repository. The Access Committee of the UK Biobank Board should be contacted if someone wants to request the data from this study. Researchers interested in accessing the UK Biobank data can apply directly through the UK Biobank online Access Management System (https://www.ukbiobank.ac.uk/). For further information on data acquisition and statistical details, please contact Dr. Youngwon Kim at youngwon.kim@hku.hk.

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References

1. Roth, G. A., Mensah, G. A. & Johnson, C. O. Global burden of cardiovascular diseases and risk factors, 1990–2019: update from the GBD 2019 study. *J. Am. Coll. Cardiol.* **76** (25), 2982–3021 (2020).
2. Nelson, C. P., Goel, A. & Butterworth, A. S. Association analyses based on false discovery rate implicate new loci for coronary artery disease. *Nat. Genet.* **49** (9), 1385–1391 (2017).
3. Ntalla, I., Kanoni, S. & Zeng, L. Genetic risk score for coronary disease identifies predispositions to cardiovascular and noncardiovascular diseases. *J. Am. Coll. Cardiol.* **73**(23), 2932–2942 (2019).
4. Barbaresko, J., Rienks, J. & Nöthlings, U. Lifestyle indices and cardiovascular disease risk: a meta-analysis. *Am. J. Prev. Med.* **55**(4), 555–564 (2018).
5. Myers, R. H., Kiely, D. K., Cupples, L. A. & Kannel, W. B. Parental history is an independent risk factor for coronary artery disease: The Framingham Study. *Am. Heart. J.* **120** (4), 963–969 (1990).
6. Kim, Y., Rangel, J. & Colabianchi, N. Food environments and cardiovascular disease: evidence from the health and retirement study.*Am. J. Prev. Med.* **67** (2), 201-209 (2024).
7. Guasch-Ferré, M., Li, Y. & Bhupathiraju, S. N. Healthy lifestyle score including sleep duration and cardiovascular disease risk. *Am. J. Prev. Med.* **63** (1), 33–42 (2022).
8. Grundy, S. M., et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: A report of the American college of Cardiology/American Heart Association task force on clinical practice guidelines. *Circulation* **139** (25), e1082–e1143 (2019).
9. Wong, N. D. Epidemiological studies of CHD and the evolution of preventive cardiology. *Nat. Reviews Cardiol.* **11** (5), 276–289 (2014).
10. Goff, D. C. Jr., Lloyd-Jones, D. M. & Bennett, G. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American college of cardiology/american heart association task force on practice guidelines. *Circulation Jun.* **24** (25 Suppl 2), S49–73 (2014).
11. group Sw, collaboration ECr. SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe. *Eur. Heart J.* **42** (25), 2439–2454 (2021).
12. Damen, J. A., Pajouheshnia, R. & Heus, P. Performance of the Framingham risk models and pooled cohort equations for predicting 10-year risk of cardiovascular disease: a systematic review and meta-analysis. *BMC Med.* **17** (1), 109 (2019).
13. Sun, L., Pennells, L. & Kaptoge, S. Polygenic risk scores in cardiovascular risk prediction: A cohort study and modelling analyses. *PLoS Med.* **18** (1), e1003498 (2021).
14. Hageman, S. H. J., Petitjean, C. & Pennells, L. Improving 10-year cardiovascular risk prediction in apparently healthy people: flexible addition of risk modifiers on top of SCORE2. *Eur. J. Prev. Cardiol.* **30** (15), 1705–1714 (2023).
15. Fry, A., Littlejohns, T. J. & Sudlow, C. Comparison of sociodemographic and health-related characteristics of UK biobank participants with those of the general population. *Am. J. Epidemiol.* **186** (9), 1026–1034 (2017).
16. Bycroft, C., Freeman, C. & Petkova, D. The UK biobank resource with deep phenotyping and genomic data. *Nature* **562** (7726), 203–209 (2018).
17. Benjamin, E. J., Blaha, M. J. & Chiuve, S. E. Heart disease and stroke Statistics-2017 update: A report from the American heart association. *Circulation Mar.* **7** (10), e146–e603 (2017).
18. Rutten-Jacobs, L. C., Larsson, S. C. & Malik, R. Genetic risk, incident stroke, and the benefits of adhering to a healthy lifestyle: cohort study of 306 473 UK biobank participants. *Bmj Oct.* **24**, 363:k4168 (2018).
19. Wallisch, C. et al. External validation of two Framingham cardiovascular risk equations and the pooled cohort equations: a nationwide registry analysis. *Int. J. Cardiol.* **283**, 165–170 (2019).
20. Refaeilzadeh, P., Tang, L. & Liu, H. Cross-validation. *Encyclopedia Database Syst.* **5**, 532–538 (2009).
21. Pencina, M. J. & D'Agostino, R. B. Overall C as a measure of discrimination in survival analysis: model specific population value and confidence interval Estimation. *Stat. Med.* **23** (13), 2109–2123 (2004).
22. Pencina, M. J., D'agostino, R. B., Pencina, K. M., Janssens, A. C. J. & Greenland, P. Interpreting incremental value of markers added to risk prediction models. *Am. J. Epidemiol.* **176** (6), 473–481 (2012).
23. Demler, O. V., Paynter, N. P. & Cook, N. R. Tests of calibration and goodness-of-fit in the survival setting. *Stat. Med.* **34** (10), 1659–1680 (2015).
24. Sushama, J. B. The role of lifestyle in development of coronary heart disease. In *Inflammatory Heart Diseases* (ed. Wilbert S.A, Takashi M.) Ch.11 (IntechOpen 2019).
25. Critchley, J. A. & Capewell, S. Mortality risk reduction associated with smoking cessation in patients with coronary heart disease: A systematic review. *JAMA* **290** (1), 86–97. https://doi.org/10.1001/jama.290.1.86 (2003).

26. Fukumoto, Y. *Lifestyle Intervention for Primary Prevention of Cardiovascular Diseases*p.2250–2251 (Oxford University Press US, 2022).
27. Aragam, K. G. & Natarajan, P. Polygenic scores to assess atherosclerotic cardiovascular disease risk. *Circul. Res.* **126** (9), 1159–1177. https://doi.org/10.1161/CIRCRESAHA.120.315928 (2020).
28. Arnold, N. & Koenig, W. Polygenic Risk Score: Clinically Useful Tool for Prediction of Cardiovascular Disease and Benefit from Lipid-Lowering Therapy? *Cardiovasc. Drugs Ther.* **35**(3), 627–635 (2021).
29. Elliott, J., Bodinier, B. & Bond, T. A. Predictive accuracy of a polygenic risk score–Enhanced prediction model vs a clinical risk score for coronary artery disease. *JAMA* **323** (7), 636–645 (2020).
30. Mosley, J. D., Gupta, D. K. & Tan, J. Predictive accuracy of a polygenic risk score compared with a clinical risk score for incident coronary heart disease. *Jama* **323** (7), 627–635 (2020).
31. Morrison, A., Voorman, A. & Johnson, A. Cohorts for heart and aging research in genetic epidemiology (CHARGE) consortium. Whole-genome sequence-based analysis of high-density lipoprotein cholesterol. *Nat. Genet.* **45** (8), 899–901 (2013).
32. Willer, C. J., Schmidt, E. M. & Sengupta, S. Discovery and refinement of loci associated with lipid levels. *Nat. Genet.* **45** (11), 1274 (2013).
33. Havulinna, A. S., Kettunen, J. & Ukkola, O. A blood pressure genetic risk score is a significant predictor of incident cardiovascular events in 32 669 individuals. *Hypertension* **61** (5), 987–994 (2013).
34. Labarthe, D. R. & Dunbar, S. B. Global cardiovascular health promotion and disease prevention. *Circulation* **125** (21), 2667–2676 (2012).
35. Rossello, X., Dorresteijn, J. A. & Janssen, A. Risk prediction tools in cardiovascular disease prevention: A report from the ESC prevention of CVD programme led by the European association of preventive cardiology (EAPC) in collaboration with the acute cardiovascular care association (ACCA) and the association of cardiovascular nursing and allied professions (ACNAP). *Eur. Heart Journal: Acute Cardiovasc. Care.* **9** (5), 522–532 (2020).
36. Lim, S. S., Semnani-Azad, Z. & Morieri, M. L. Reporting guidelines for precision medicine research of clinical relevance: the BePRECISE checklist. *Nat. Med.* **30** (7), 1874–1881 (2024).
37. Hutcheon, J. A., Chiolero, A. & Hanley, J. A. Random measurement error and regression Dilution bias. *Bmj.* **340**, (2010).
38. Roth, G. A., Mensah, G. A. & Johnson, C. O. Global burden of cardiovascular diseases and risk factors, 1990-2019: Update from the GBD 2019 study. *J. Am. Coll. Cardiol.* **76** (25), 2982–3021 (2020).
39. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012. The fifth joint task force of the European society of cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). Developed with the special contribution of the European association for cardiovascular prevention & rehabilitation (EACPR). *Eur. J. Prev. Cardiol.* **19** (4), 585–667 (2012).

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Author contributions

QS contributed to the study design, performed the statistical analyses and drafted the manuscript. HJ conceptualised this study, designed the analysis plan, and performed the statistical analyses. MW contributed to data management and quantification of key covariates, including PRS and some lifestyle behaviours. SLAY and SL helped generate the PRS variables. YK contributed to the study design. YK conceptualised this study, curated data, provided resources and funding needed for the conduct of this study, critically interpreted the study findings, and provided multiple sets of critical revisions. All authors helped interpret the study findings, critically reviewed and approved the final version of the manuscript, and agreed to be responsible for all facets of this work. YK is the guarantor.

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Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

The UK Biobank was approved by the North-West Multi-Centre Research Ethics Committee (Ref: 11/NW/0382). The present study was approved by the Institutional Review Board of The University of Hong Kong/ Hospital Authority Hong Kong West Cluster (UW 21–542).

Additional information

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