Temporal trends in cardiovascular risk factors and performance of the Framingham Risk Score and the Pooled Cohort Equations

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► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/jech-2018-211102).

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Received 28 May 2018
Revised 1 August 2018
Accepted 31 August 2018
Published Online First 27 September 2018

ABSTRACT

Background The Framingham Risk Score (FRS) and the Pooled Cohort Equations (PCE) are established tools for the prediction of cardiovascular disease (CVD) risk. In the Western world, decreases in incidence rates of CVD were observed over the last 30 years. Thus, we hypothesise that there are also temporal trends in the risk prediction performance of the FRS and PCE from 1990 to 2000.

Methods We used data from n=7789 men and women aged 40–74 years from three prospective population-based cohort studies enrolled in Southern Germany in 1989/1990, 1994/1995 and 1999/2000. 10-year CVD risk was calculated by recalibrated equations of the FRS or PCE. Calibration was evaluated by percentage of overestimation and Hosmer-Lemeshow tests. Discrimination performance was assessed by receiver operating characteristic (ROC) curves and corresponding area under the curve (AUC).

Results Across the three studies, we found significant temporal trends in risk factor distributions and predicted risks by both risk scores (men: 18.0%, 15.4%, 14.9%; women: 8.7%, 11.2%, 10.8%). Furthermore, also the discrimination performance evolved differently for men (AUC PCE: 76.4, 76.1, 72.8) and women (AUC PCE: 75.9, 79.5, 80.5). Both risk scores overestimated actual CVD risk.

Conclusion There are temporal trends in the performance of the FRS and PCE. Although the overall performance remains adequate, sex-specific trends have to be taken into account for further refinement of risk prediction models.

BACKGROUND

Cardiovascular disease (CVD) is a leading cause of mortality and morbidity worldwide.[1]

To reduce the burden of CVD, prevention strategies such as lifestyle counselling and treatment with medication are called for and have to be tailored to the population at risk. For effective prevention, people at a high risk of CVD who would benefit most from these strategies have to be identified. This is often done by predicting the risk of developing CVD based on an individual's risk factor levels, such as age, blood pressure or serum cholesterol levels. Risk prediction models are crucial tools for establishing general treatment guidelines. However, they are also used by clinicians to decide on the best therapy for an individual patient.

A vast number of CVD risk prediction models are available nowadays, and their number is constantly growing.[2] Often the development of a new model is motivated by the claim that, as existing models have been calculated from older data, they fail to capture the changing distribution of risk factors in the population. Indeed, the distribution of traditional risk factors and metabolic profiles in Western populations changed during the last decades. Specifically, mean systolic blood pressure has decreased, probably due to increased awareness and more aggressive treatment.[3] The prevalence of smoking has decreased with considerable variation according to region and education status[4] and total cholesterol levels have declined with age-specific and sex-specific variations.[5] At the same time, the prevalence of obesity has risen substantially for both men and women.[6]

Additionally, total cardiovascular mortality has been declining in the USA and Europe.[7] However, it remains unclear how this shifting risk factor distribution and reduction of overall risk translates into changes in the performance of risk prediction models. We therefore aimed to assess temporal trends in traditional cardiovascular risk factors and how their changing distribution relates to a change in risk prediction performance. To this aim, we analyse 10-year risks of CVD predicted by the Framingham Risk Score (FRS)[8] and the Pooled Cohort Equations (PCE).[9]

We hypothesise that changes in risk factor distributions are reflected in a changing performance of the CVD risk scores.

METHODS

Study sample

We used data from three population-based cohorts that were established in the Region of Augsburg, Germany (KORA: 'Kooperative Gesundheitsforschung in der Region Augsburg'). Time of data collection was 1989–1990 for cohort S2, 1994–1995 for cohort S3 and 1999–2000 for cohort S4. Sampling methods and cohort profiles have been described elsewhere.[10 11] All cohorts were followed up for mortality and for myocardial infarction (MI) and stroke incidence until 2011. For each cohort, we used 10 years of follow-up to calculate the risk scores. Participants were excluded according to criteria for FRS and PCE as presented in online supplementary figure 1: in particular we only analysed subjects aged 40–74 years.

Outcome assessment

Death from CVD was defined as International Classification of Diseases, ninth revision codes 390–459

To cite: Rospleszcz S, Thorand B, de las Heras Gala T, *et al*. *J Epidemiol Community Health* 2019;**73**:19–25.

and 798. Death certificates were obtained to determine the cause of death.

Non-fatal MI and stroke incidence was assessed by questionnaire and validated by reviewing the medical documentation of the participant's physician. MI was additionally validated with the information from the MONICA/KORA Myocardial Infarction Registry.[12]

Covariable assessment

Blood pressure and serum cholesterol measurements for the S2 and S3 studies were carried out according to the MONICA Manual as described elsewhere.[10] For the S4 study, blood pressure was measured after a 15-min rest using a validated automatic device (OMRON HEM 705-CP). Serum total and high-density lipoprotein cholesterol (HDL-C) were measured by enzymatic methods (CHOD-PAP; Boehringer, Mannheim).[11 13]

Diabetes was defined as self-reported diabetes or use of anti-diabetic medication. Antihypertensive treatment was defined according to the most recent guidelines of the German Hypertension Society.[14] Smoking and intake of lipid-lowering agents was determined via questionnaire.

Statistical methods

Predicted 10-year risks were calculated according to the published formulae for FRS and PCE[8 9] with recalibration. Both FRS and PCE are based on Cox proportional hazard regression models and predict the risk of experiencing a cardiovascular event over a 10-year period. The published formulae provide the regression model coefficients and use risk factor mean values and baseline survival probabilities from the original populations to derive a risk score estimate. For our analysis, recalibration consisted of inserting risk factor mean values and baseline survival probabilities from each study into the original risk score equations, while maintaining the original model coefficients. Thereby, the original model structure, including sex stratification, non-linear model terms and interaction terms are retained and within this original framework, the recalibration only reflects the specific properties of the sample at hand. We tested for linear trends in baseline characteristics and predicted 10-year risks with linear and logistic regression using orthogonal contrasts.[15]

Calibration of the risk scores was assessed visually by calibration plots and quantitatively by Hosmer-Lemeshow χ^2tests, calibration slopes and % discordance between the number of observed and predicted events.[16] Clinically relevant thresholds of 5, 7.5, 10% and 20% were used, as well as continuous calibration curves based on LOESS smoothing.[17]

Discrimination performance was assessed by receiver operating characteristic (ROC) curves and their respective area under the curve (AUC), which is equivalent to the c-statistic.[18] Differences in AUCs over time were evaluated by an unpaired DeLong test. Additionally, we report Somer's D statistic, which indicates the rank correlation between predicted risk probabilities and observed event rate. For relevant thresholds, sensitivity was calculated and differences were assessed by meta-regression assuming fixed effects.[19] Population-attributable fractions (PAFs) of risk scores ≥20% or ≥10% as opposed to risk scores <20% and <10%, respectively, were calculated by Levin's formula with CIs obtained by percentile bootstrapping. We use the term 'attributable' without implying causality.

RESULTS

Trends in risk factor distributions

Table 1 shows the baseline characteristics of the participants of all three studies.

Mean age was similar across all studies for both men and women. There was a significant trend for increasing body mass index (BMI) for both men and women.

Mean systolic blood pressure decreased for both men and women, but more pronounced in women. The proportion of men receiving antihypertensive treatment increased significantly.

There was no significant linear trend in mean HDL-C levels. Mean total cholesterol levels and mean low-density lipoprotein cholesterol (LDL-C) levels declined significantly for both sexes. The proportion of both men and women receiving lipid-lowering treatment increased significantly.

Table 1 Baseline characteristics of participants in Kooperative Gesundheitsforschung in der Region Augsburg S2 (1989–1990), S3 (1994–1995) and S4 (1999–2000)

	Men					Women				
	S2	S3	S4	Linear trend		S2	S3	S4	Linear trend	
	n=1432	n=1332	n=1139	Estimate	P values	n=1360	n=1322	n=1204	Estimate	P values
Age, years	55.8 (9.7)	56.6 (9.6)	56.0 (9.5)	0.10	0.70	55.7 (9.4)	55.4 (9.7)	55.4 (9.6)	−0.24	0.36
BMI, kg/m^2	27.6 (3.6)	27.8 (3.5)	28.0 (3.9)	0.30	<0.05	27.0 (4.7)	27.4 (4.9)	27.5 (4.9)	0.34	<0.05
Systolic BP, mm Hg	138.1 (18.4)	138.7 (18.8)	136.8 (18.4)	−0.87	0.09	133.6 (20.2)	134.0 (20.6)	127.0 (19.5)	−4.66	<0.05
Diastolic BP, mm Hg	83.2 (11.2)	83.9 (11.3)	84.7 (10.7)	1.04	<0.05	79.9 (10.8)	80.3 (10.9)	79.4 (10.2)	−0.35	0.25
Total cholesterol, mg/dL	245.0 (44.5)	238.8 (42.6)	236.1 (41.1)	−6.29	<0.05	245.9 (46.5)	237.4 (42.4)	235.8 (41.1)	−7.19	<0.05
HDL-C, mg/dL	51.6 (15.2)	48.5 (14.1)	51.5 (14.2)	−0.03	0.95	63.8 (15.9)	59.9 (16.8)	64.5 (17.2)	0.53	0.26
LDL-C, mg/dL	155.3 (40.5)	149.8 (40.3)	148.4 (38.9)	−4.90	<0.05	152.6 (44.4)	145.6 (41.6)	141.8 (40.1)	−7.62	<0.05
Type 2 diabetes	83 (5.8%)	67 (5.0%)	74 (6.5%)	0.09	0.46	59 (4.3%)	43 (3.3%)	58 (4.8%)	0.08	0.56
Antihypertensive treatment	229 (16.0%)	232 (17.4%)	218 (19.1%)	0.15	<0.05	268 (19.7%)	266 (20.1%)	266 (22.1%)	0.10	0.14
Lipid-lowering treatment	50 (3.5%)	43 (3.2%)	73 (6.4%)	0.45	<0.05	41 (3.0%)	56 (4.2%)	82 (6.8%)	0.60	<0.05
Smoking	400 (27.9%)	331 (24.8%)	274 (24.1%)	−0.14	<0.05	219 (16.1%)	230 (17.4%)	209 (17.4%)	0.06	0.39
CVD event	177 (12.4%)	139 (10.4%)	119 (10.4%)	−0.13	0.13	60 (4.4%)	76 (5.7%)	67 (5.6%)	0.17	0.18
Fatal CVD event	106 (7.4%)	62 (4.7%)	46 (4.0%)	−0.45	<0.05	36 (2.6%)	31 (2.3%)	28 (2.3%)	−0.01	0.61

Continuous variables are presented as arithmetic mean (SD). Categorical variables are presented as counts (%). CVD event is defined as death from CVD, non-fatal MI and stroke.
BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction.

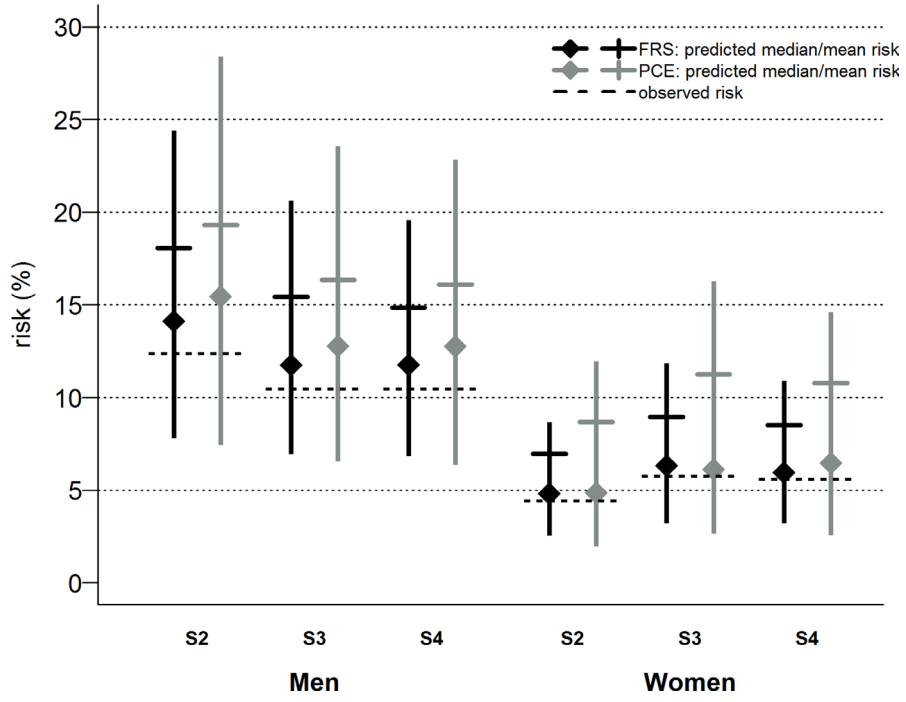

Figure 1 Predicted risks by Framingham Risk Score (FRS) and Pooled Cohort Equations (PCE). On the y-axis: risk of cardiovascular disease event in %. On the x-axis: FRS (black) and PCE (grey) for the three studies, for men (dashed lines) and women (solid lines), respectively. Displayed are the median (filled diamond) and mean (cross) predicted risks with interquartile range as calculated by the recalibrated equations of the FRS and PCE. Actually observed risk is indicated by a dashed line.

The prevalence of diabetes slightly increased non-linearly for both men and women. Prevalence of smoking significantly decreased in men and increased slightly in women.

There was no significant trend in CVD event rates, though they slightly declined for men and increased for women. However, fatal CVD event rates were significantly declining for men.

Trends in predicted risks of the FRS and PCE

Figure 1 shows mean and median predicted risk for both risk scores and the actually observed event rate. Mean predicted risks by both FRS and PCE declined significantly for men (estimate of linear trend: both −2.3, p<0.001), but increased for women (estimate of linear trend FRS 1.1, PCE 1.5, p<0.001).

Trends in calibration of the FRS and PCE

Both the FRS and PCE substantially overestimated actual CVD risk. Discordance for the FRS was 46%, 48% and 42% for men in the three studies, respectively, whereas for women discordance was 58%, 55% and 53%. Discordance for the PCE was 56%, 57% and 54% for men and 96%, 96% and 94% for women. Smooth calibration plots are displayed in figure 2, and further details are presented in online supplementary figure 2 and table 1. Overall, the FRS showed better calibration for men and women and calibration slightly improved for both the FRS and PCE in the three studies. Calibration slopes for the FRS were 1.07, 1.13 and 0.97 for men and 0.99, 1.14 and 1.00 for women, whereas calibration slopes for the PCE were 1.01, 1.11 and 0.87 for men and 0.81, 0.93 and 0.90 for women.

Trends in discrimination performance of the FRS and PCE

As shown in figure 3, for men, the discrimination performance of both the FRS and PCE declined from the S2 to the S4 study; however, the difference in AUC was not statistically significant (p=0.232 and 0.223, respectively). In contrast, for women the discrimination performance increased for both the FRS and PCE; however, the difference in AUC was not significant (P=0.749 and 0.220, respectively). In the S4 study, the difference in AUC between men and women was statistically significant for the PCE (p=0.02), but not for the FRS (p=0.12).

In the same vein, Somer's D rank correlation for the FRS decreased from 0.53 in S2 and S3 to 0.46 in S4 in men and increased from 0.54 to 0.55 and 0.57 in women. Corresponding values for the PCE were 0.53, 0.52 and 0.46 for men and 0.52, 0.59 and 0.61 for women, respectively.

The sensitivity at clinically relevant thresholds decreased for men and increased for women; again for both risk scores in a similar pattern as presented in table 2.

Trends in PAFs

The evolvement of PAFs is displayed in figure 4. For men, the PAF of a risk score ≥20% or ≥10% declined from the S2 to the S4 study for both risk scores. For women, the PAF of a risk score ≥10% increased over the three studies, whereas the PAFs of a risk score ≥20% were more divergent: The PAF of an FRS ≥20% was comparable in the S2 and S4 study, but the PAF of a PCE ≥20% increased in the same time frame.

DISCUSSION

In this study, we evaluated temporal trends in the distribution of traditional cardiovascular risk factors in a German population and in the performance of two commonly employed CVD risk scores, the FRS and the PCE. We found (i) significant trends in risk factor distributions with declining levels of systolic blood pressure and lipid values and increasing BMI for both men and women, (ii) significant trends in predicted risks for both FRS and PCE, and (iii) sex-specific differences in the temporal development of the risk scores' performance with nominally decreasing performance for men and increasing performance for women.

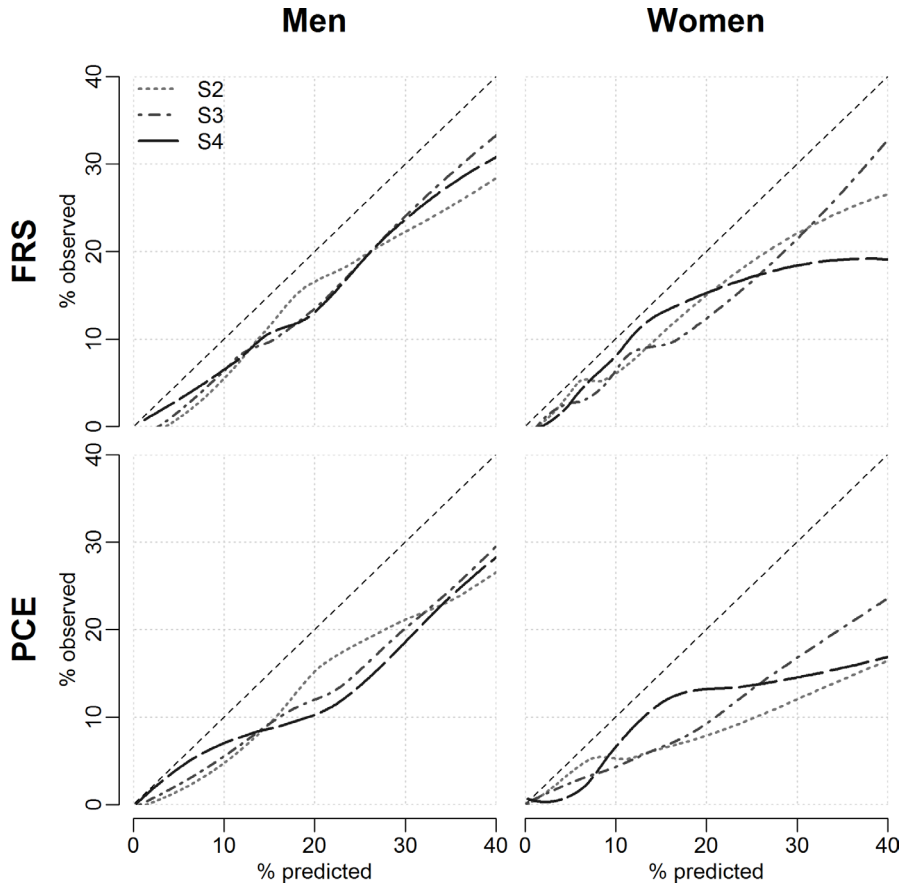

Figure 2 Smooth calibration of the Framingham Risk Score (FRS) and Pooled Cohort Equations (PCE) in the three studies. On the x-axis: predicted probability of cardiovascular disease (CVD) event by the respective risk score, calculated by LOESS smoothing. On the y-axis: rate of observed CVD events. Light grey, dotted line: S2 study; medium grey, dashed-and-dotted line: S3 study, dark grey, dashed line: S4 study. This figure was created by an adapted version of the the R function val.prob.ci.2 from Van Calster *et al*.[17]

Overall, the FRS and the PCE evolved over time in a similar pattern. We observed fundamental overestimation of actual CVD risk, especially for the PCE. This has already been reported by other studies[20–22] and seems to indicate an inherent feature of the design of the PCE.[23] We could show that calibration slightly increased over time; however, not to a substantial extent. This development was comparable for men and women.

Trends in predicted risks can give important hints about future CVD development in a population. Ford[15] analysed predicted CVD risks by the FRS in six consecutive 2-year cycles of the National Health and Nutrition Examination Survey and found decreasing predicted risks in white subjects; however, the decrease was not significant and men and women were combined. No data on actual CVD events were available.

In our analysis, the change in absolute numbers of predicted risk resulted into sex-specific changes in prediction performance of the risk scores. We observed a decline in AUC for men and an increase for women. However, in all studies and for both men and women, the discrimination performance of both risk scores as measured by AUC was >70.

It has been noted that risk prediction models perform differently for men and women.[24] Women develop CVD later in life and the strength of associations of some risk factors, especially smoking and diabetes, are different.[25 26] In our sample, although CVD risk was lower for women, both risk scores performed better than for men. These findings were also reported from other studies[27] and are probably due to higher hazard ratios of the single underlying risk factors.

Our analysis of the PAF showed that high-risk categories (≥10%, ≥20%) of both risk scores capture a major part of CVD burden. For women, the PAF increased over time, supporting our other findings of a developing better discrimination performance of the risk models for women. Further research is needed to disentangle the effects of the single risk factors that contribute to the risk scores. Cheng *et al*, who analysed data from the ARIC cohort, found that due to a shifting risk factor distribution the PAF of most traditional risk factors was declining for both men and women with profound sex differences.[28]

Our results support the idea that established models derived from older population- based data still perform sufficiently well in risk prediction, if appropriately adapted to the population at hand.[2 29]

We used standardised measurement techniques on independent cohorts with the same study design and sampling scheme with the same length of follow-up. These cohorts stem from the same geographical area and therefore comprise the same genetic background. This design has the advantage—compared with using the same cohort at different time points—that we can rule out ageing effects, survivor bias and longitudinal dependencies of risk factor profiles in subjects.

Our study has several limitations. Most importantly, we might have had insufficient power to discover some differences due to the low event rate, especially in women. Replication of our findings in a population with higher CVD event rates is therefore needed. The possibility of residual confounding cannot be ruled out. Additionally, we cannot exclude that different response

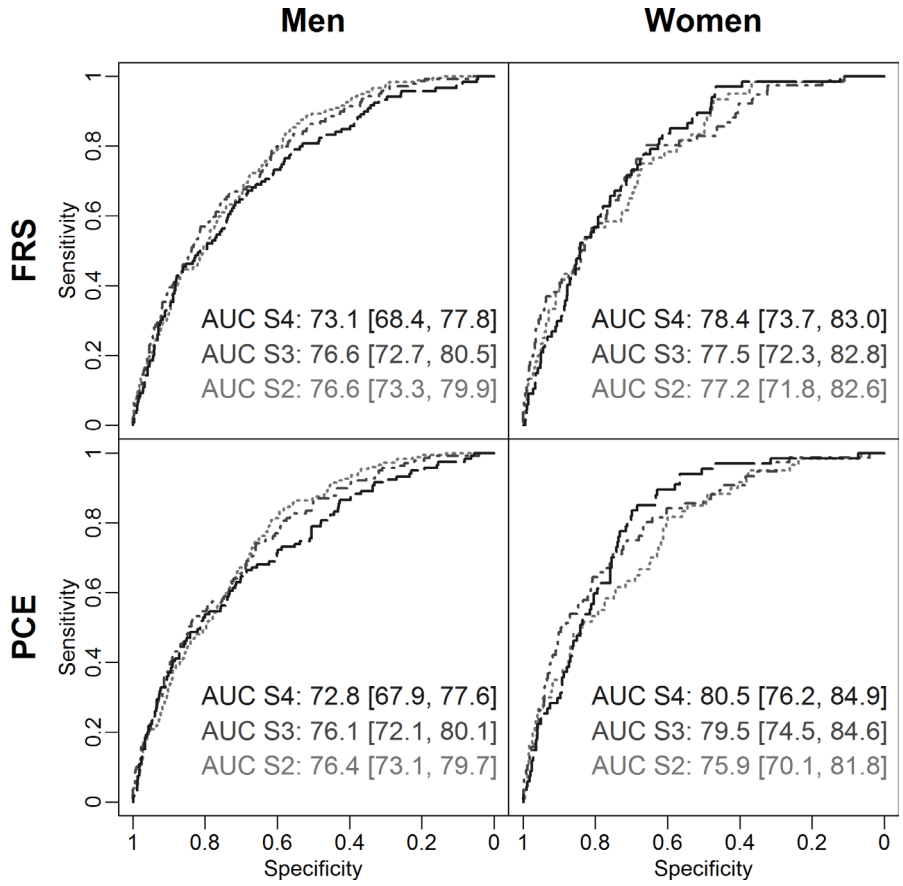

Figure 3 Receiver operating characteristic (ROC) curves and area under the curve (AUC) for Framingham Risk Score (FRS) and Pooled Cohort Equations (PCE) in the three studies. Displayed are the ROC curves and corresponding AUC when the respective risk score is used as the only predictor for a CVD event. Light grey, dotted: S2 study; medium grey, dashed-and-dotted: S3 study; dark grey, dashed: S4 study.

rates in the three cohorts affected the distribution of the participants' risk factors. However, potential incomplete ascertainment of CVD events does not seem to have profound influence on the risk scores' performance.[30] Furthermore, we refrained from reporting other common measures of model assessment, such as the Net Reclassification Index, as this measure is mainly used to compare an extended model to a baseline model to quantify the potential improvement in risk performance, or positive predictive values (PPVs), as these are highly dependent on the rate of CVD events, which differ between our three cohorts, thus rendering a comparison of PPVs invalid.

Many other CVD risk scores exist besides the FRS and PCE. For European populations, SCORE[31] is often used; however, this score only predicts CVD mortality. Using only fatal CVD events would have further diminished our already low event rate (compare table 1); therefore, we did not analyse the performance of SCORE in this study. Other commonly used risk scores such as PROCAM,[32] Reynolds Risk Score[33 34] and QRISK2[35] require

Table 2 Performance of the Framingham Risk Score (FRS) and Pooled Cohort Equations (PCE) at clinically relevant thresholds in Kooperative Gesundheitsforschung in der Region Augsburg S2, S3 and S4

		FRS						PCE					
		7.5%		10%		20%		7.5%		10%		20%	
Threshold		Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
Men													
Sensitivity	S2	98.3	95.1 to 99.6	94.4	89.9 to 97.3	66.1	58.6 to 73.0	97.2	93.5 to 99.1	94.4	89.9 to 97.3	75.7	68.7 to 81.8
	S3	96.4	91.8 to 98.8	89.2	82.8 to 93.8	59.7	51.1 to 67.9	95.7	90.8 to 98.4	89.9	83.7 to 94.4	65.5	56.9 to 73.3
	S4	93.3	87.2 to 97.1	83.2	75.2 to 89.4	52.1	42.8 to 61.3	91.6	85.1 to 95.9	86.6	79.1 to 92.1	60.5	51.1 to 69.3
	P values	0.079		0.008		0.054		0.085		0.068		0.015	
Women													
Sensitivity	S2	61.7	48.2, 73.9	55.0	41.6 to, 67.9	20.0	10.8 to 32.3	71.7	58.6 to 82.5	61.7	48.2 to 73.9	35.0	23.1 to 48.4
	S3	80.3	69.5, 88.5	71.1	59.5 to 80.9	36.8	26.1 to 48.7	84.2	74.0 to 91.6	80.3	69.5 to 88.5	57.9	46.0 to 69.1
	S4	80.6	69.1, 89.2	67.2	54.6 to 78.2	25.4	15.5 to 37.5	91.0	81.5 to 96.6	85.1	74.3 to 92.6	47.8	35.4 to 60.3
	P values	0.019		0.135		0.079		0.014		0.005		0.03	

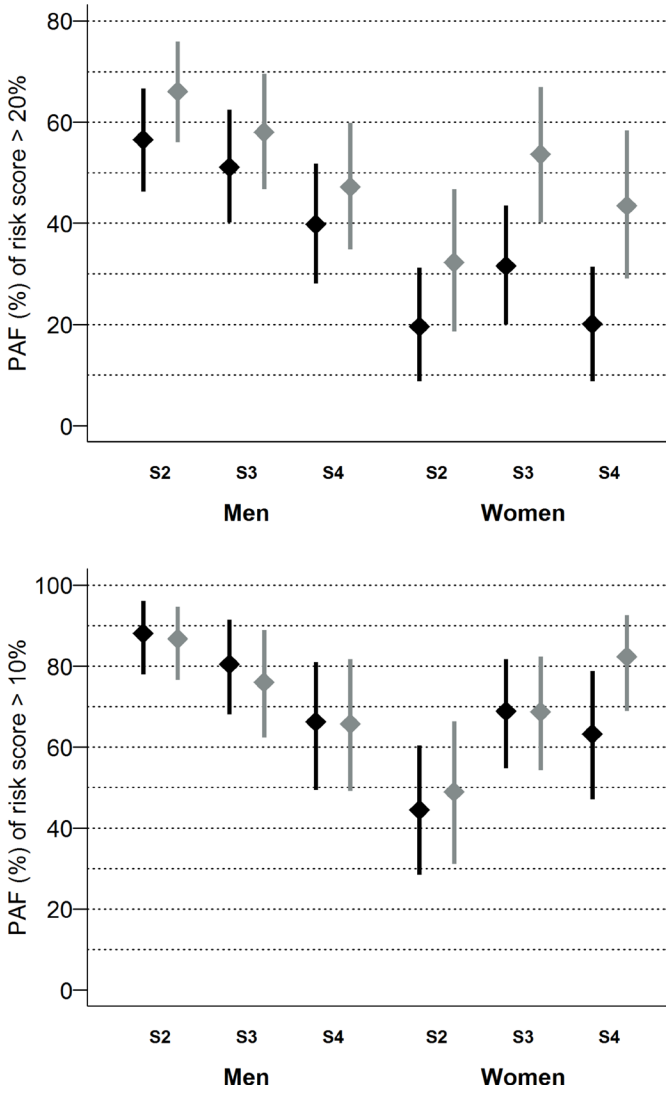

Figure 4 Trends in population-attributable fractions (PAFs). On the y-axis: PAF of a predicted risk of ≥ 20% (above) or ≥ 10% (below) as compared to a predicted risk <20% (above) or <10% (below) in % with respective 95% CIs. On the x-axis: all three studies, men and women, Framingham Risk Score (black), Pooled Cohort Equations (grey).

additional variables, such as family history of CVD, C-reactive protein or measures of deprivation, which were not readily available in all of our cohorts.

In conclusion, risk models have to be modified to the population at hand to maximise their clinical utility. Particular attention has to be paid to refining sex-specific risk predictions. Our results show that the performance of both the FRS and the PCE is susceptible to changes in the underlying risk factor distributions and event rates; however, the overall performance of the risk scores is still adequate and the underlying risk factors capture a major part of the burden of CVD.

What is already known on this subject

- Risk scores based on the Framingham Equations and the Pooled Cohort Equations are commonly used tool to predict cardiovascular disease (CVD) risk.
- These scores rely on traditional cardiovascular risk factors such as age, blood pressure and lipid profile.
- The distribution of these risk factors has shifted in the last decades in Western populations and CVD incidence has decreased.

What this study adds

- We used three independent studies to analyse the impact of a shifting risk factor distribution on the performance of both risk scores.
- We found temporal trends in the amount of predicted risk as well as in the discrimination performance.
- We found a sex-specific temporal evolvement, with improving discrimination performance in women and decreasing performance in men.
- These sex-specific differences should be more strongly taken into account for the future refinement and development of prediction models.

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Contributors SR derived the study questions, conducted the statistical analyses and interpretation of results and drafted the manuscript. BT, TdlHG, CM, RH and WK participated substantially in the data acquisition and quality control of the cohort data used for the study, reviewed the manuscript and revised it for important intellectual content. UM contributed substantially to the statistical analyses of the manuscript, reviewed the manuscript and revised it for important intellectual content. AP contributed substantially to the design of the study questions, participated substantially in the data acquisition and quality control of the cohort data used for the study, reviewed the manuscript and revised it for important intellectual content. All authors have approved the final manuscript.

Funding The KORA study was initiated and financed by the Helmholtz Zentrum München – German Research Center for Environmental Health, which is funded by the German Federal Ministry of Education and Research (BMBF) and by the State of Bavaria.

Competing interests None declared.

Patient consent Not required.

Ethics approval The KORA studies were approved by the ethics committee of the Bavarian Chamber of Physicians, Munich. The investigations were carried out in accordance with the Declaration of Helsinki.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The informed consent given by KORA study participants does not cover data posting in public databases. However, data are available upon request from KORA-gen (http://epi.helmholtz-muenchen.de/kora-gen/) by means of a project agreement. Requests should be sent to kora.passt@helmholtz-muenchen.de and are subject to approval by the KORA Board.

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