

The value of additional risk factors for improving 10-year cardiovascular risk prediction in apparently healthy people

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Background: In clinical practice, factors known to be associated with cardiovascular disease (CVD) like albuminuria, education level, or coronary calcium score are not directly incorporated in cardiovascular risk prediction models. The aim of the current study was to quantify the added value of potential risk modifying characteristics when added to the SCORE2 algorithm for individuals without diabetes mellitus (DM) or prior CVD.

Methods and results: Individuals without previous CVD or DM were included from the ARIC, MESA, EPIC-NL and HNR studies (n=46,285) in whom 2,177 CVD events and 2,062 non-cardiovascular deaths were observed over exactly 10.0 years of follow-up. The effect of each possible risk modifying characteristic was derived using Fine and Gray models that included an offset term for the SCORE2 linear predictor. The risk modifying characteristics were applied to individual predictions using the “naïve approach”, which modifies predicted risks based on the population prevalence and the SHR of the relevant predictor. Subdistribution hazard ratios are presented in the table. External validation was performed in the

CPRD cohort (UK, n=518,015, 12,675 CVD events). In the external validation, adjustment of SCORE2 predicted risks with both single and with all available risk modifiers did not negatively affect calibration (see figure) and led to a modest increase in discrimination (C-index 0.742 [95% CI 0.737–0.746] versus unimproved SCORE2 risk C-index 0.737 [95% CI 0.732–0.741]). The net reclassification index or adding all these predictors was +0.032 (95% CI 0.025; 0.028) for future events and –0.008 (95% CI –0.009; –0.007) for future non-events. The coronary calcium score was found to the single strongest added predictor.

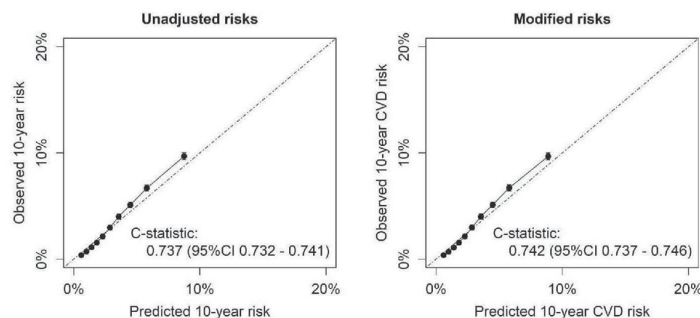
Interpretation: The current analysis presents a method on how to integrate possible risk modifying characteristics that are not included in existing CVD risk models for the prediction of CVD event risk in apparently healthy people. This flexible methodology improves the accuracy of predicted risks and increases applicability of prediction models for individuals with additional risk known modifiers

Table: Subdistribution hazard ratios of the additional risk factors

Predictor	sHR (95% CI)
Ankle brachial index (<0.9)	1.28 (1.03-1.59)
Body mass index (kg/m ²)†	1.02 (0.96-1.09)
Coronary calcium Agatston-percentile†	1.91 (1.60-2.21)
History of cancer	1.17 (0.94-1.44)
Carotid stenosis (>25%)	1.59 (1.26-2.01)
Carotid intima media thickness (mm)‡	1.01 (0.91-1.12)
Estimated GFR (ml/min/1.73m ²)†	1.03 (0.93-1.18)
hsCRP (mg/L)†	1.32 (1.05-1.67)
History of chronic inflammatory disease	0.95 (0.54-1.67)
Lower education level	1.28 (1.16-1.41)
Parental history of myocardial infarction	1.34 (1.19-1.51)
Former smoking (versus never)	1.12 (1.01-1.25)
Gestational hypertension	1.17 (0.98-1.39)
Lp(a) (mg/dL)†	1.13 (0.93-1.36)
Albuminuria (>30mg/g)	1.91 (1.60-2.28)
Number of drugs (n)‡	1.18 (1.10-1.26)
NT-ProBNP (pg/ml)*	1.48 (1.38-1.58)
Troponin-T (pg/ml)*	1.53 (1.42-1.66)

Predictors marked with (*) are log-transformed, predictors marked with (†) are squared, and predictors marked with (‡) are linear. For all these continuous predictors, the subdistribution hazard ratios are presented as 3rd versus 1st quartile. GFR = glomerular filtration rate (calculated with Chronic Kidney Disease Epidemiology Collaboration [CKDEPI] formula), CAC= coronary calcium score, hsCRP = high sensitivity C-reactive protein, Lp(a) = lipoprotein(a), NT-proBNP = N-terminal pro-B-type natriuretic peptide.

Figure: External validation in the real-world data of CPRD using all available risk modifiers (n=517,595)



Calibration in the CPRD data shown for the original low risk region SCORE2 model (left) and after reclassification using all available information on risk modifying characteristics in this real-world dataset (right).