External validation of two Framingham cardiovascular risk equations and the Pooled Cohort equations: A nationwide registry analysis

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ABSTRACT

Background: Cardiovascular prevention guidelines advocate the use of statistical risk equations to predict individual cardiovascular risk. However, predictive accuracy and clinical value of existing equations may differ in populations other than the one used for their development. Using baseline and follow-up data of the Austrian health-screening program, we assessed discrimination, calibration, and clinical utility of three widely recommended equations—the Framingham 1991 and 2008 general cardiovascular disease (CVD) equations, and the Pooled Cohort equations predicting atherosclerotic CVD.
Methods: The validation cohort comprised 1.7 M individuals aged 30–79, without documented CVD history who participated in the program from 2009 to 2014. CVD events were defined by a cardiovascular cause of hospitalization or death.
Results: The observed five-year general CVD risk was 4.66%. Discrimination c-indices (0.72–0.78) were slightly lower than those reported for the development cohorts. C-indices for women were always higher than for men. CVD risk was overestimated by the Framingham 2008 equation, but underestimated by the Pooled Cohort equations. The Framingham 1991 equation was well-calibrated, especially for individuals up to 64 years. If applied to recommend health interventions at a predicted five-year risk between 5 and 10%, the equations were clinically useful with their net benefits, weighting true positives against false positives, ranging from 0.13 to 3.43%.
Conclusion: The equations can discriminate high-risk from low-risk individuals, but predictive accuracy (especially for high-risk individuals) might be improved by recalibration. The Framingham 1991 equation yielded the most accurate predictions.

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1. Introduction

While the incidence of cardiovascular disease (CVD) has declined since the 1970s, particularly in high-income regions [1], CVD remains the leading cause of morbidity and mortality. It accounted for 37% of all deaths in the European Union in 2014 [2]. CVD risk is associated with factors such as smoking or blood cholesterol, which are potentially modifiable via lifestyle changes or medication [3,4]. However, for primary or secondary prevention it is crucial that individuals are made aware of the contributions of risk factors to their personal CVD risk. Therefore, assessment of CVD risk on the basis of the combined effect of various risk factors using statistical risk equations is recommended in guidelines on CVD prevention [5,6]. Several CVD risk equations have been developed and their validity has been assessed in similar populations. However, the properties of prediction tools may differ across settings and populations, thus rendering their performance and clinical utility uncertain. External validation studies have already shown that risk equations often over- or underestimate the observed risk in other populations possibly due to a different case-mix, regional differences, or changes in treatment [7–12].

In Austria, a country with mandatory and near-universal health care coverage [13], the Main Association of the Austrian Social Security Institutions (MAASSI) offers an annual preventive health-screening examination at no cost to all of its adult residents. One of the objectives of the program is to assess CVD risk using the New Zealand Risk Scale

and the American Heart Association Risk Calculator [14,15]. For individuals with increased CVD risk an intervention in the form of a lifestyle consultation and, where needed, pharmacological therapy are recommended [15]. However, both risk equations, used in the screening program, have not been validated in the Austrian population.

Therefore, we designed the present study to evaluate the properties of three widely-accepted CVD prediction tools in the Austrian general population, using the data on all residents participating in the Austrian national health-screening program.

2. Methods

2.1. The Austrian health-screening program

Using information on health-screenings, the validation cohort included all 2,159,616 individuals, a third of the Austrian population from 30 to 79 years (2011), who underwent a preventive health-screening between 01-2009 and 03-2014. The pseudonymized data set provided by MAASSI included the health-screenings registry, and information on any hospital admissions or deaths of screened individuals recorded between 01-2009 and 03-2015. Health-screening variables were: demographic data (age, sex), laboratory values (e.g., total cholesterol), systolic blood pressure (BP) and BP-lowering medication, self-reported smoking status, and comorbidities. Distributions of BP and blood parameter measurements were truncated at the respective 0.5th and 99.5th percentiles. Missing values in BP treatment (8.1%) were assumed to indicate no treatment. The otherwise low proportion of missing values in risk factors (0.07% of all individuals) allowed a complete-case analysis. From hospitalization records, date of admission, duration, and main discharge diagnosis according to the 9th or 10th revision of the International Classification of Diseases (ICD) were recorded. Causes of death were obtained by linkage with the registry of deaths from Statistics Austria (the Austrian federal institute for Statistics). A probabilistic assignment of CVD or non-CVD-related death had to be applied to 10.3% of the CVD outcomes. The study protocol conforms to the ethical guidelines of 1975 Declaration of Helsinki as reflected in a priori approval by the ethics committee of the Medical University of Vienna.

2.2. Evaluated risk equations

We externally validated the following CVD risk equations for primary prevention in the general population for a five-year time horizon: the Framingham 1991 general CVD (FR1991) equation which is also used in the New Zealand Risk Scale [14,16], the Framingham 2008 general CVD (FR2008) equation, [17] and 2013 atherosclerotic CVD (ASCVD) Pooled Cohort (PC) equations from the American College of Cardiology (ACC)/American Heart Association (AHA) [5]. After literature research on CVD risk equations, we selected these as they require information which is recorded during a health-screening. We excluded the SCORE equation predicting CVD death because a probabilistic assignment was used for causes of death and this may influence the results for risk equations focusing only on hard endpoints [18]. Key characteristics of the chosen equations and their development cohorts are summarized in Table S1. All equations use these traditional CVD risk factors: sex, age, blood pressure (BP), total and high-density lipoprotein (HDL) cholesterol, diabetes, and smoking status. The validation set comprised 1,684,012 individuals, included at their first screening, who were between 30 and 79 years, free of documented CVD (starting 01-2008), and had a potential follow-up of at least one year (Fig. S1). An appropriate subset of this validation set was used for each equation according to its exclusion criteria. The exclusion criteria limit the age range for which the equation was developed and exclude individuals with certain diseases defined by ICD codes. Details on all methodical issues and the exact exclusion criteria can be found in Methods S1.

2.2.1. Framingham 1991 equation
The Framingham study was the first to investigate cardiovascular risk in a well-constructed, though relatively small cohort (n = 5573). The original 1991 equation is one of the best known risk equations for combined fatal and non-fatal general CVD risk over a ten-year time horizon [16].

2.2.2. Framingham 2008 equation
The FR1991 equation was revised in 2008 using an extended Framingham cohort (n = 8491) [17]. While keeping the original outcome definition and time horizon, the exclusion criteria were slightly changed (Table S1).

2.2.3. Pooled Cohort equations
As part of the 2013 Guideline on the Assessment of Cardiovascular Risk, the ACC and AHA developed this equation for the prediction of ten-year ASCVD [5]. In the present study, the equation for non-Hispanic whites was applied.

2.3. Statistical analysis

We used median and interquartile range (IQR) to summarize continuous variables and absolute frequencies and percentages for categorical variables. Mean linear predictors in the development and validation cohorts were used to assess the degree of relatedness

between cohorts [19]. Differences in mean linear predictors reflect the difference in overall predicted outcome frequencies. We evaluated discrimination, the ability of a risk equation to distinguish between individuals at low or high risk, calibration, the agreement between observed cumulative incidences and predicted probabilities, and clinical utility using decision curves [20]. Discrimination for the five-year risk was assessed by Uno's cumulative c-index, which is an equivalent of the area under the curve of a receiver-operating curve [21]. It states the probability that a randomly chosen individual with CVD has a higher predicted probability then another randomly chosen individual without CVD. Calibration was visualized by plotting predicted probabilities against observed incidence rates for each decile of predicted risk including confidence intervals. Observed incidence rates were calculated by Kaplan-Meier estimation at the five-year risk for each decile. The predicted/observed-ratio (P/O ratio) was derived by the mean model-based prediction divided by the Kaplan-Meier estimate for five-year risk. Decision curves visualize the net benefit of applying a risk equation to guide treatment decisions. The net benefit is defined as the true positive rate minus a weighted false positive rate at a given threshold probability triggering treatment decisions. For general CVD events within ten years, the suggested threshold probabilities are in the range of 10–20%, or equivalently 5–10% for an event within five years [6,17,22,23]. An intuitive explanation of decision curves was given by Vickers et al. [24]. Additionally, we evaluated discrimination and calibration for low- and high-risk groups.

While sufficient discrimination of a risk equation is a basic requirement, calibration is even more relevant in the context of external validation, as the degree of calibration can vary considerably between different populations. Only for sufficiently discriminating and well-calibrated risk equations clinical utility is of interest.

3. Results

Baseline characteristics of the 1,684,012 individuals of the validation cohort are given in Table 1. Median age was 50 (IQR 41, 61). Women had slightly more favorable distributions with regard to traditional CVD risk factors than men, e.g., they had a lower HDL/total cholesterol ratio, a lower prevalence of diabetes, smoked less often, and received BP medications less often. Median follow-up time was 4.00 (2.67, 5.00) years for individuals included in the validation of both Framingham equations, and 4.08 (2.75, 5.00) for the PC equations. We observed 0.93 general CVD events per 100 patient-years in the FR1991 validation set, 0.94 in the FR2008 validation set, and 1.18 ASCVD events per 100 patient-years in the PC equations validation set.

3.1. Framingham 1991 equation

The 1,575,614 individuals from the validation set who matched the inclusion criteria of the FR1991 equation were similar to the original development cohort with regard to systolic BP, total and HDL cholesterol (Table S2). However, they were less likely to have diabetes (4.76% Austrian, 6.05% Framingham) and less likely to be smokers (22.73%, 39.73%). Overall, the mean linear predictors in both cohorts were similar.

Table 1

Baseline characteristics and observed five-year CVD and ASCVD risk of individuals in the validation set.

Median (interquartile-range, IQR) or n (%) are stated. Statistical tests comparing women and men were all highly significant due to the large size of the data set (all $p < 0.001$).

	Women (n = 905,806; 53.8%)	Men (n = 778,206; 46.2%)
Age	50 (41, 62)	50 (41, 61)
Total cholesterol (mmol/L)	5.40 (4.73, 6.15)	5.35 (4.65, 6.08)
HDL cholesterol (mmol/L)	1.60 (1.34, 1.91)	1.27 (1.06, 1.53)
Cholesterol ratio	3.3 (2.7, 4.1)	4.2 (3.4, 5.1)
Systolic BP (mm Hg)	125 (115, 140)	130 (120, 141)
BP treatment	127,529 (14.1)	119,239 (15.3)
Smoking	182,808 (20.2)	187,896 (24.2)
Diabetes	40,293 (4.5)	48,910 (6.3)
Observed five-year risk in % as defined by		
Framingham 1991 general CVD ($n_{events} = 55,078$)	3.29	6.17
Framingham 2008 general CVD ($n_{events} = 56,380$)	3.31	6.25
Pooled Cohort equations ASCVD ($n_{events} = 60,219$)	4.32	7.49

Table 2

Quantifying discrimination using c-indices.

The time horizon indicates for which time interval the predicted risk was estimated. As it is usually the case, externally validated c-indices were smaller than c-indices of the development cohorts.

Equation	Cohort	Time horizon (years)	C-index Women	C-index Men
Framingham 1991 general CVD equation[a]	*Validation Austria*	5	0.772	0.759
Framingham 2008 general CVD equation	Development	10	0.793	0.763
	Validation Austria	5	0.771	0.762
Pooled Cohort equations for ASCVD[b]	Development Non-Hispanic whites	10	0.806	0.746
	Validation Contemporary	10	0.738	0.684
	Validation MESA[c]	6	0.711	0.704
	Validation REGARDS[d]	4	0.750	0.661
	Validation Austria	5	0.778	0.719

[a] No c-index was reported in the original publication [16].
[b] The model for non-Hispanic whites was used; c-indices were reported in the supplement of Goff et al. [5].
[c] Multi-Ethnic Study of Atherosclerosis.
[d] REasons for Geographic And Racial Differences in Stroke study.

The observed five-year risk for general CVD was 3.29% for women and 6.17% for men with 0.65 and 1.26 general CVD events per 100 patient-years, respectively. The discrimination c-index for the five-year risk was 0.772 for women and 0.759 for men (Table 2). With regard to calibration, observed CVD incidences agreed well with predictions from the FR1991

equation (Fig. 1a). The P/O ratios for women and men (1.04 and 1.09) were close to the optimum value of 1. For individuals from 30 to 59 years, the FR1991 equation predicted the observed event rates very well (Fig. 2). However, for individuals >64 years, we observed an increase in observed CVD events which was not reflected in the predictions.
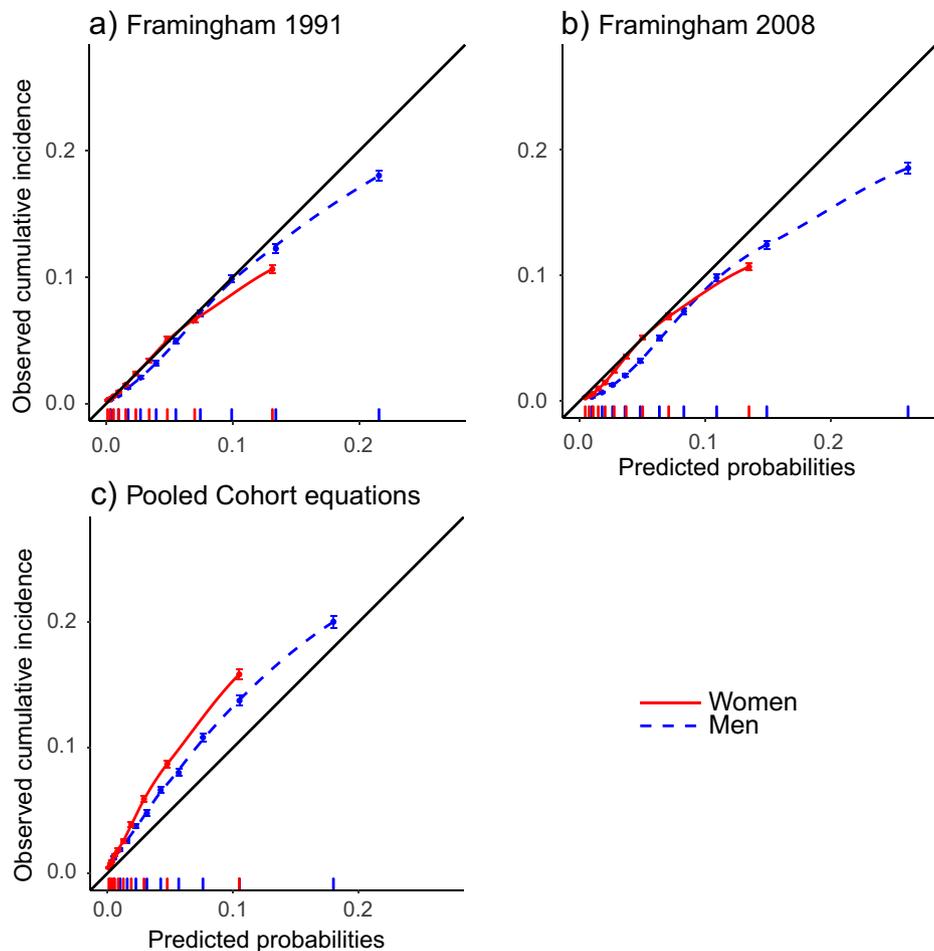

Fig. 1. Calibration plots for a) the Framingham 1991, b) the Framingham 2008 equations, and c) the Pooled Cohort equations. The calibration curves for women and men are shown in red (solid line) and blue (broken line). Error bars represent 95% confidence intervals. The distribution of the predicted probabilities is given on the x-axis. While the FR1991 equation slightly overestimates the CVD risk for individuals in the highest decile of predicted risk, the overestimation of CVD risk is more pronounced in the FR2008 equation. The PC equations underestimate the ASCVD risk.
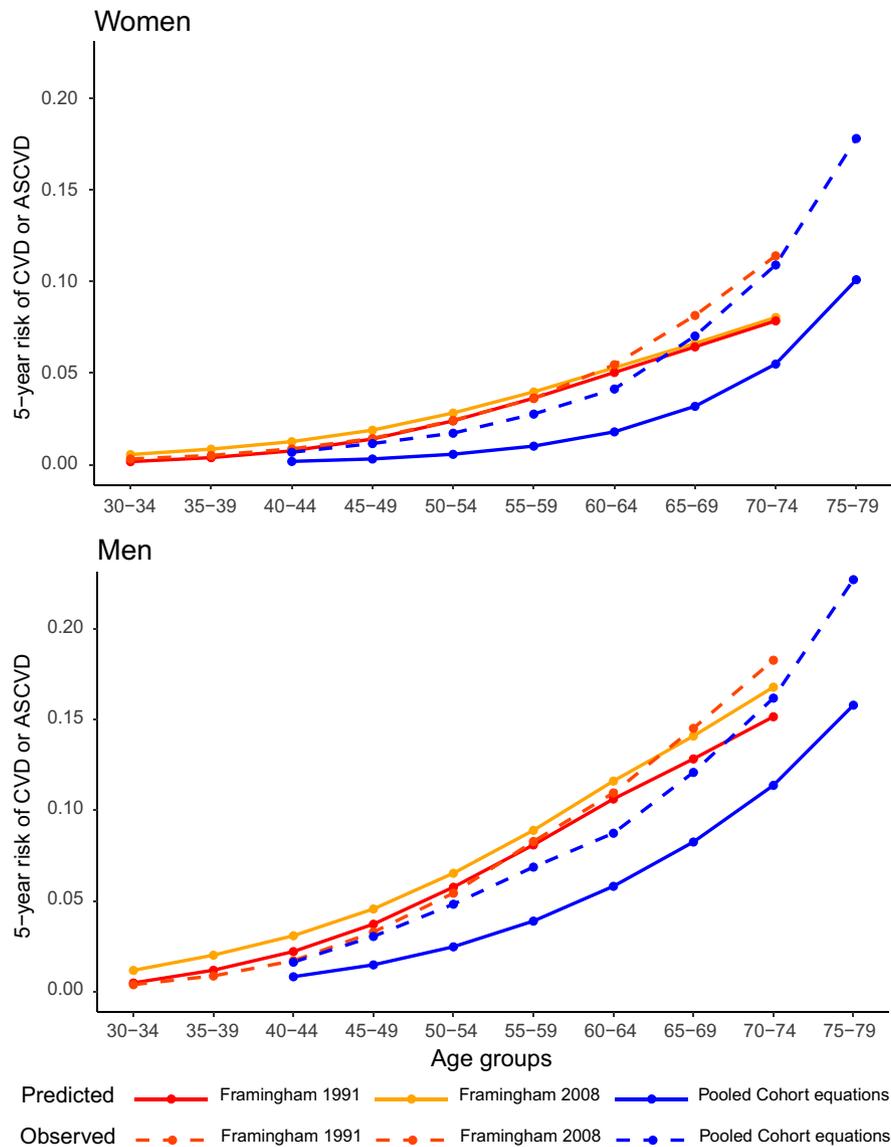
Women

Men

Fig. 2. Median predicted five-year CVD risk for different age groups for the Framingham 1991 and 2008 equations and the Pooled Cohort equations.

3.1.1. Net benefit of applying the equation

Assessment of clinical utility at a threshold probability of 10% (for the five-year CVD risk) revealed a net benefit of 0.13% and 1.16% for women and men (Fig. S2). This indicates that the equation correctly predicted 12 additional CVD incidences per 1000 men without increasing the number of false detections. By this threshold, we assume that failing to avoid a CVD incidence by early intervention is nine times worse than performing unnecessary interventions [20]. At this threshold probability, the net benefit of the equation is 7.59% for women and 5.24% for men greater than assuming all individuals will experience a CVD event within five years. Hence, we can reduce 680 and 490 unnecessary interventions per 1000 women and 1000 men by applying the equation. For a threshold probability of 5% (one missed necessary intervention being equivalent to 19 performed unnecessary interventions), the net benefit was 0.79% for women and 2.90% for men.

3.2. Framingham 2008 equation

The validation set for the FR2008 equation contained all individuals who met the inclusion criteria of the FR1991 equation plus 21,597 individuals with a diagnosis of cancer at baseline. For women and men, 0.66 and 1.27 CVD events per 100 patient-years were observed. The c-indices

at five years were 0.771 and 0.762 (Table 2) and hence similar to the originally reported ones [17]. Calibration curves indicated a slight overestimation of the CVD risk, especially for men (Fig. 1b). P/O ratios were 1.14 and 1.29 for women and men. For women <60 years and men <65 years, the predicted CVD risk was consistently too high (Fig. 2). By contrast, for women aged ≥65 the predicted risk was considerably too low.

3.2.1. Net benefit of applying the equation

At threshold probabilities from 5 to 10%, the net benefit of the FR2008 equation is almost identical to the net benefit of the FR1991 equation (Fig. S2). This means that for a threshold probability of 5% the equation correctly predicted 1 and 29 additional CVD incidences per 1000 women and 1000 men without increasing the number of false detections. At this threshold probability, the number of unnecessary interventions can be reduced by 490 per 1000 women and by 300 per 1000 men.

3.3. Pooled Cohort equations

The PC equations validation subset included 1,337,475 individuals from 40 to 79 years. The observed five-year risk for ASCVD was 4.32%

for women and 7.49% for men; 0.87 ASCVD events per 100 patient-years were observed for women and 1.54 for men. The mean linear predictors of the development cohort and the Austrian validation set were similar (Table S2). C-indices for the five-year risk for women and men (0.778 and 0.719) were smaller than the c-indices for ten-year risk of the development cohort, but higher than c-indices from other validation cohorts (Table 2) [5]. Calibration plots indicated underestimation over the whole range of predicted probabilities, even for individuals with low predicted probabilities (Fig. 1c). For men, the PC equation was slightly better calibrated. P/O ratios were 0.54 for women and 0.73 for men. Underestimation of the PC equations was more pronounced in older individuals, especially in women (Fig. 2). Even for younger individuals aged 40–44 some underestimation was evident.

3.3.1. Net benefit of applying the equation

At threshold probabilities from 5 to 10% the PC equations exhibited net benefits from 1.34–0.41% for women and 3.43–1.43% for men (Fig. S2). Use of the equation for threshold probabilities from 5 to 10% would lead to a reduction of 390–600 unnecessary interventions in women who will not develop ASCVD within five years without an increase in the number of untreated women who will develop ASCVD. For men a reduction of 150–380 unnecessary interventions could be achieved for the same range of threshold probabilities.

3.4. Generalization to the Austrian population

Risk assessment for CVD is primarily of interest when individuals undergo health-screenings. Nevertheless, we investigated if the results of this study could be generalized to the Austrian general population (8,388,534 inhabitants [2011]). Our validation set represents 32.5% of the Austrian population aged 30–79. It is representative of the general population with regard to sex distribution, smoking habits and diabetes, and has a similar overall survival as the general population (Table S3). However, individuals in their 70s were underrepresented in the validation set, and those who underwent health-screenings had a slightly better overall five-year survival rate than the general population.

4. Discussion

Using the records of ~1.7 M Austrian individuals participating in the free national health-screening program, we validated the Framingham 1991 and 2008 general CVD equations and the ASCVD Pooled Cohort equations. This external validation study revealed acceptable discrimination as all c-indices exceeded 0.71. The observed five-year risk for CVD was 4.7%. While both Framingham equations slightly overestimated the average CVD risk, they underestimated the risk in individuals older than 64 years. The PC equations systematically underestimated the five-year risk, irrespective of stratification by predicted risk or age groups.

The discriminative abilities of the FR1991, the FR2008 and the PC equations were higher in our population than in some other external validation studies [7,9,25,26]. As expected, in an external validation results on calibration depend to a large extend on the similarity of the development to the validation cohort. In consistence with our results, Milne et al., who investigated the FR1991 equation, found accurate prediction of CVD risk for the population in New Zealand [8]. As observed by Zomer et al. [7], we also found that the Framingham equations overestimated CVD risk and that the FR2008 equation yielded higher predictions than the FR1991 equation. External validation studies of the PC equations gave mixed results. While Muntner et al. observed good calibration in a validation cohort similar to the development cohorts [9], overestimation of ASCVD risk was observed in other cohorts [10,27]., Whereas we found that ASCVD risk was underestimated in the Austrian validation cohort.

Using decision analysis methodology, we showed that the three equations exhibited a net benefit at threshold probabilities ranging from 5 to 10% for women and men. A threshold probability of 5% for the five-year general CVD-risk (or equivalently 10% for the ten-year risk) was suggested by the AHA for women as well as by European guidelines [6,23]. Generic hydroxymethyl glutaryl coenzyme A reductase inhibitors (statins) are already cost-effective at this threshold [23]. A threshold probability of 10% for the five-year CVD-risk was used in US guidelines predicting general CVD for drug treatment [17,22]. Although setting a threshold for characterizing high-risk individuals is arbitrary, it is necessary for decision making. Setting higher thresholds will leave a large portion of high-risk individuals untreated, while lower thresholds will increase costs of treatment and cost-effectiveness (pharmacological treatment or lifestyle changes).

4.1. Strengths and limitations

This contemporary validation study included a large part of the Austrian population and comprised ~6.5 M person-years of follow-up. All participants of the Austrian health-screening program (from 2009 to 2014) complying with the inclusion criteria of the three equations were included. We applied no additional criteria for selecting individuals, thus maximizing its generalizability. Participation in a health-screening program naturally implies self-selection. Therefore, our study cohort was on average slightly younger and had a marginally better survival rate than the general population. Currently, health-screening uses CVD risk charts to inform individuals about their risk. Thus, CVD risk factors are routinely evaluated in participants and entered into the registry in a standardized and reproducible way at the time of examination. We focused on equations with non-fatal and fatal CVD endpoints, as both are of interest for individuals and physicians. Results of this external validation may be generalized to populations similar to this one with a comparable public health system.

Despite of the advantages of our study design, results should be interpreted in view of their limitations. As electronic recording of the health-screening program started in 2009, we evaluated CVD risk only with a horizon of five years, in line with other studies [9,26]. For the FR2008 equation, only ten-year baseline survival was reported and thus we approximated the five-year value assuming a constant hazard over time. Comparing the historic Framingham cohorts with our contemporary one, increased awareness of CVD risk, i.e., changes in utilization of antihypertensive and lipid-lowering medication and of lifestyle, might explain some of the residual overestimation of the Framingham equations. In addition, our self-selected cohort is likely to comply even more with these preventative measures. Some fatal CVD events may have been misclassified because of our probabilistic assignment of causes of death in case of ambiguity. Lastly, mild cases of CVD may have been missed in hospital discharge diagnoses.

4.2. Conclusions

Modern medicine relies on CVD risk equations to raise awareness and to support the prevention of CVD. In this large Austrian cohort, we found that the Framingham equations overestimated general CVD risk, while the Pooled Cohort equations underestimated the ASCVD risk. The Framingham 1991 equation yielded the most accurate predictions. Therefore, we recommend applying this equation in the health screening program. However, in order to avoid the risks of unnecessary pharmacological overtreatment and the consequences of missed CVD prevention, we also recommend recalibrating these risk equations, especially the Framingham 2008 equation and the Pooled Cohort equation.

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Conflicts of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.11.001.

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