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ORIGINAL ARTICLE

Health 2000 score – development and validation of a novel cardiovascular risk score

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ABSTRACT

Background: Previous risk scores for predicting myocardial infarctions and strokes have mainly been based on conventional risk factors. We aimed to develop a novel improved risk score that would incorporate other widely available clinical variables for predicting the broadest range of endpoints, including revascularizations.

Methods: A nationwide sample of 5843 Finns underwent a clinical examination in 2000–2001. The participants were followed for a median of 11.2 years for incident cardiovascular events. Model discrimination and calibration were assessed and internal validation was performed.

Results: Sex, age, systolic blood pressure, total cholesterol, HDL cholesterol, smoking status, parental death from cardiovascular disease, left ventricular hypertrophy, hemoglobin A1c, and educational level remained significant predictors of cardiovascular events ($p \leq 0.005$ for all). The share of participants with $\geq$10% estimated cardiovascular risk was 28.9%, 18.5%, 36.9% and 23.8% with the Health 2000, Finrisk, Framingham and Reynolds risk scores. The Health 2000 score (*c*-statistic: 0.850) showed superior discrimination to the Framingham (*c*-statistic improvement: 0.021) and Reynolds (*c*-statistic improvement: 0.007) scores ($p < 0.001$ for both comparisons). Model including left ventricular hypertrophy, hemoglobin A1c, and educational level improved the model prediction (*c*-statistic improvement: 0.006, $p = 0.003$).

Conclusions: The Health 2000score improves cardiovascular risk prediction in the current study population.

KEY MESSAGES

- Previous risk scores for predicting myocardial infarctions and strokes have mainly been based on conventional risk factors.
- We aimed to develop a novel improved risk score that would incorporate other widely available clinical variables (including left ventricular hypertrophy, hemoglobin A1c, and education level) for predicting the broadest range of endpoints, including revascularizations.
- The Health 2000 score improved cardiovascular risk prediction in the current study population compared with traditional cardiovascular risk prediction scores.

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Cardiovascular diseases; coronary revascularization; prevention; risk assessment; risk prediction; statistical models

Introduction

Cardiovascular disease remains the leading cause of death in developing and developed countries (1). One of the most important cornerstones of cardiovascular disease prevention is to identify individuals at high risk of cardiovascular disease as early as possible. On the population and individual level, the key to success is the use of reliable, cost effective and feasible cardiovascular risk assessment tools.

The majority of previous cardiovascular risk scores, such as the Framingham or Systematic Coronary Risk Evaluation (SCORE), have been based on conventional risk factors such as age, sex, cholesterol, blood pressure, diabetes mellitus, smoking status and body mass index (BMI) (2). In addition, most previous calculators have used either cardiovascular death or a composite event consisting of coronary and cerebrovascular mortality and morbidity, as endpoints. Only a few risk calculators have included coronary revascularizations as endpoints (2) although the number of revascularizations currently exceeds the number of myocardial infarctions per year in the United

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States (3). As patients' risk factor profiles are profoundly altered after coronary interventions through initiation of aggressive drug therapy, the ideal risk-prediction algorithm should contain the broadest range of clinically relevant endpoints, including revascularizations.

It has been recently reported that traditional risk assessment based on the Framingham or SCORE calculators could under- or overestimate the absolute cardiovascular risk (4,5). In addition, recent studies have shown that addition of family history of cardiovascular disease and high-sensitivity C-reactive protein in risk prediction models may improve discrimination (4,6). For efficient cardiovascular risk management, modifiable risk factors should be identified, and health-counselling and treatment should focus on individuals with high cardiovascular risk (7).

The purpose of this study was to develop a novel improved risk score that, in addition to conventional risk factors, would incorporate other widely available variables for prediction of the broadest range of cardiovascular endpoints, including coronary revascularizations.

Materials and methods

Study population

The study sample was drawn from the participants of a multidisciplinary epidemiological survey, the Health 2000 Study, which was carried out in Finland from autumn 2000 to spring 2001. The study population was a stratified nationwide 2-stage cluster sample of 8028 subjects drawn from the population register to represent Finnish adults aged $\geq$30 years. The details of stratification and sampling procedures have been reported previously (8,9).

Seventy-nine percent (n = 6354) of the individuals agreed to participate in the interview and attended the health examination. Of these participants, 301 had a prevalent cardiovascular disease, and were removed from the analyses. In addition, there were 210 subjects who had one or more variable of missing baseline data (educational level, smoking status, office blood pressure, smoking status, missing ECG data, or incomplete laboratory values). After removing individuals with at least one exclusion factor (n = 511), the study population consisted of 5843 participants aged 30–97 years. The study protocol of the Health 2000 Study was approved by the epidemiology ethics committee of the Helsinki and Uusimaa hospital region, and all of the participants gave signed, informed consent.

Flow of the study

At an initial health interview at the participant's home, basic background and sociodemographic information, information about health and illnesses were gathered by centrally trained interviewers. A physical examination was performed 1–6 weeks later at a local health center by centrally trained doctors and nurses. Each participant's height, weight and body circumference were measured, and fasting blood samples for serum lipids and glucose were taken from the participants. Digital 12-lead electrocardiographic (ECGs) were recorded with Marquette MAC 5000 (GE Marquette Medical Systems, Milwaukee, WI, USA). ECG measurements were performed in a blinded fashion with Magellan software (GE Marquette Medical Systems, Milwaukee, WI, USA) (10). Details of the methodology of the project have been published elsewhere (8,9).

Definitions and measurements

Serum high sensitivity C-reactive protein (hs-CRP) was analyzed with an automated analyzer (Optima, Thermo Electron Oy, Vantaa, Finland) and an ultrasensitive immunoturbidimetric test (Ultrasensitive CRP, Orion Diagnostica, Espoo, Finland). The limit of quantitation of the assay was 0.20 mg/L. Education level was defined as: (1) lower education (persons with no occupational degree or high school degree); (2) mid-level education (persons with an occupational or high school degree, but without a college-level degree); (3) higher education (persons with at least college-level education). Diabetes mellitus was defined as a fasting serum glucose level higher or equal to 7.0 mmol/l or the use of insulin injections, oral hypoglycemic agents or both. Smoking was defined as current use of tobacco products (yes or no). ECG-LVH was defined as a Cornell voltage (S wave in V_3 + R wave in aVL +8 mm for women) over 28 mm or a Sokolow–Lyon index S wave in V_1 + tallest R wave in V_5 or V_6 over 35 mm. Blood pressure was measured by a nurse with a conventional, calibrated, mercury sphygmomanometer from the sitting individual's right arm after a 10-min rest. Means of two measurements performed at a 2-min interval were used to determine blood pressure.

Follow-up

Follow-up data were accumulated until 31 December 2011. Non-fatal events during the follow-up were identified using the National Hospital Discharge Register, which covers all periods of treatment received in Finnish hospitals. The Hospital Discharge Register is

maintained by the government and comprehensively includes all public and private inpatient care in hospitals and institutions in Finland, including ongoing care. Fatal events were identified from the nationwide Causes of Death Register. Diagnoses are registered in these registers by the treating physicians with codes defined in the 10th revision of the International Classification of Diseases (ICD-10). Cardiovascular diagnoses in these registers, used as described below, have been described and validated in detail previously (11–13). Acute nonfatal coronary events were identified with ICD-10 codes I20– I22 and/or if the participant had underwent percutaneous coronary intervention or coronary artery bypass surgery. For fatal coronary events, ICD-10 codes I20-I25, I46, R96 and R98 were used. Stroke diagnoses in ICD-10 were I60-I61 and I63-I64 (not I63.6). The primary end point was one of the following: cardiovascular mortality, nonfatal myocardial infarction, nonfatal stroke, percutaneous coronary intervention and coronary artery bypass surgery. Only the first event was included in the analysis.

Statistical analyses

We examined the associations between cardiovascular events and potential cardiovascular risk, and constructed the Health 2000 risk score equation using a Cox regression model. The linearity of the predictors was tested by first categorizing each quantitative predictor into fifths and then comparing the likelihood ratio tests of the Cox models with this predictor as categorical or linear. Risk estimates for the study population were also calculated using the previously published equations for the Reynolds, Framingham and Finrisk scores (6,14–16).

Diabetic subjects were removed from the analyses when the cardiovascular risk of the Health 2000 score was compared with the Reynolds score as the Reynolds score cannot be calculated for diabetic men. We compared model discrimination with *c*-statistics, the net reclassification index and the integrated discrimination index (17,18). Net reclassification index categories were 5%, 10% and 20%. Calibration plots were calculated in deciles to visually compare observed and predicted risk across the risk scores. Model calibration was also tested using the Hosmer–Lemeshow goodness-of-fit test in deciles of risk. Recalibration was performed to compare the Finrisk, Framingham and Reynolds scores because of differences in end-points. The models were recalibrated so that the average risk estimates (the models were adjusted for baseline hazard and mean linear predictor) produced by the Health 2000, Finrisk, Framingham and the Reynolds models were equal (calibration-in-the-large) (19). Internal cross-validation using 100 repetitions was performed in the Health 2000 study cohort with a randomly selected 70% training sample and 30% validation sample to determine the model validity (20). In the bootstrap resampling the model was fitted in a sample (n = 5843) drawn with replacement from the original data using 100 repetitions. Database management and statistical analysis were performed with SAS software (SAS Institute, Cary, North Carolina, USA), version 9.3.

Results

The baseline characteristics of the study population are reported in Table 1. The median follow-up was 11.2 years (mean 10.2 ± 2.0 years, fifth to 95th percentile interval 5.9–11.3 years). Of the 5843 study participants 557 had suffered a cardiovascular event.

Table 1. Characteristics of the study population.

Risk Factor	Total (n = 5843)	CV event (n = 557)	No CV event (n = 5286)
Men, %	44.8	54.6	43.8
Age,y, mean (SD)	51.9 (14.5)	67.2 (13.5)	50.3 (13.6)
BMI, kg/m^2, mean (SD)	26.9 (4.6)	28.0 (4.5)	26.8 (4.6)
Current smoking, %	21.9	21.2	21.9
Diabetes mellitus, %	5.2	15.8	4.1
Systolic BP, mm Hg, mean (SD)	134.2 (21.0)	148.3 (23.5)	132.8 (20.2)
Total cholesterol, mmol/l, mean (SD)	6.0 (1.1)	6.3 (1.2)	5.9 (1.1)
HDL cholesterol, mmol/l, mean (SD)	1.3 (0.4)	1.2 (0.4)	1.4 (0.4)
GHb-A1c, %, mean (SD)	5.3 (0.7)	5.7 (1.0)	5.3 (0.6)
hs-CRP, mg/l, mean (SD)	2.2 (6.0)	3.7 (8.7)	2.0 (5.6)
Family history of cardiovascular deaths*, %	28.3	42.2	26.9
Cornell voltage, mV, mean (SD)	15.0 (6.1)	17.6 (6.5)	14.8 (6.0)
Education level, %			
Lower level	37.9	65.7	35.0
Medium level	32.9	23.2	33.9
Higher level	29.3	11.1	31.2
Antihypertensive medication, %	7.1	9.7	6.9

BP: blood pressure; BMI: body mass index; CV: cardiovascular; HDL: high density lipoprotein; MI: myocardial infarction; hs-CRP: high sensitivity C-reactive protein.
*Parental death from cardiovascular disease.

Model specification

Multivariate Cox regression models were used to estimate the associations between risk factors and cardiovascular events. First, we included 14 potential risk factors based on clinical knowledge and previous studies in the models. Of these covariates, the following reached statistical significance: sex, age, systolic BP, total cholesterol, HDL cholesterol, smoking status, parental death of myocardial infarction or stroke, ECG-LVH by Cornell criteria, GHb-A1c and degree of education ($p < 0.002$ for all). High-sensitivity CRP, BMI or use of antihypertensive medication were not predictive of cardiovascular events in this model ($p > 0.16$ for all). Second, we included only significant covariates in the final model (Table 2). GHb-A1C and ECG-LVH defined with Cornell criteria were included in the model instead of a diabetes status and ECG-LVH defined with the Sokolow–Lyon index because of strong multicollinearity and a greater improvement in the model goodness-of-fit. Third, we calculated the equation for the Health 2000 risk score for a cardiovascular event with Cox regression (Supplementary material).

Predicted risk estimates and model calibration

The average crude risk for a cardiovascular event using the Health 2000, Finrisk, Framingham and Reynolds risk scores was 9.5%, 6.0%, 10.9% and 7.9%, respectively. The crude risk estimates of the Health 2000, Finrisk, Framingham and Reynolds risk scores are presented in Figure 1. The share of participants with ≥5% estimated cardiovascular risk was 46.0%, 30.4%, 58.4% and 37.5% with the Health 2000, Finrisk, Framingham and Reynolds risk scores, respectively. The corresponding values for ≥10% risk were 28.9%, 18.5%, 36.9% and 23.8% in the 4 models, and the corresponding values for ≥20% risk were 15.0%, 8.1%, 15.8% and 12.3% in the 4 models, respectively. The models were recalibrated for the comparison of the model discrimination so that the average risk of a cardiovascular event equaled that of the Health 2000 risk score (9.5%). We assessed the calibration of the Health 2000, Finrisk, Framingham and Reynolds risk scores by comparing the predicted recalibrated cardiovascular risk with the observed cardiovascular events (Figure 2). The Hosmer–Lemeshow tests indicated poor calibration for the recalibrated Finrisk ($\chi^2 = 18.2$, $p = 0.02$),

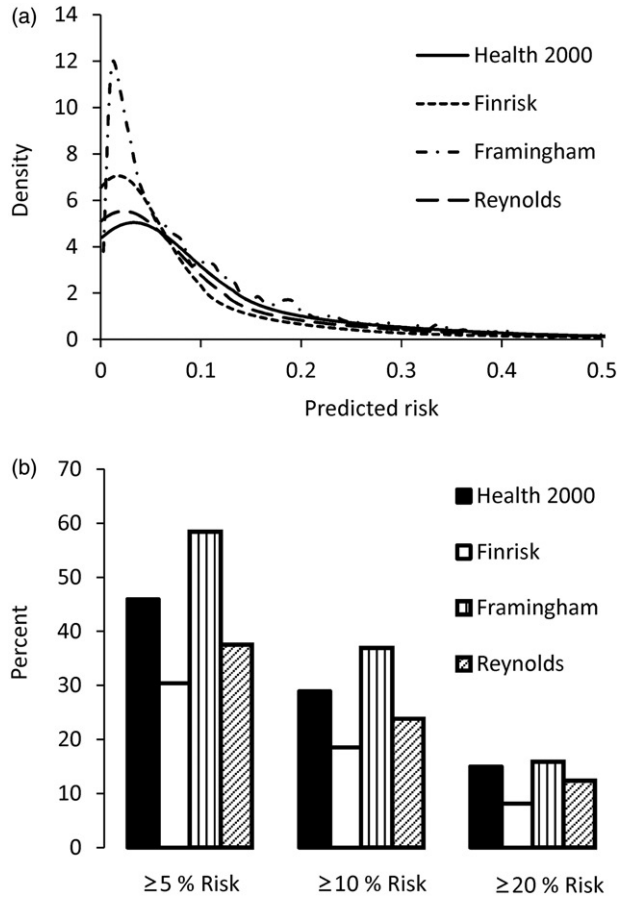

Figure 1. (a) Distribution of estimated absolute risk using the Health 2000, Finrisk, Framingham and Reynolds risk scores. (b) Estimated share of participants with ≥5%, ≥ 10% and ≥20% absolute cardiovascular risk using the Health 2000, Finrisk, Framingham and Reynolds risk scores.

Table 2. Cox cardiovascular event risk model based on the Health 2000 study.

Variable	Parameter estimate (SE)	p	Hazard ratio (95% CI)
Systolic BP, (increase of 1 mm Hg)	0.00668 (0.002)	0.001	1.007 (1.003–1.011)
Cornell volts, (increase of 1 mm)	0.01626 (0.006)	0.005	1.016 (1.005–1.028)
Total cholesterol, (increase of 1 mmol/l)	0.15114 (0.037)	<0.001	1.163 (1.081–1.251)
HDL cholesterol (increase of 1 mmol/l)	−0.48029 (0.131)	<0.001	0.619 (0.478–0.800)
Sex (0 = female, 1 = male)	0.60003 (0.091)	<0.001	0.549 (0.459–0.654)
Age, (increase of 1 year)	0.07059 (0.004)	<0.001	1.073 (1.065–1.081)
Smoking status (0 = non-smoker, 1 = current smoker)	0.61718 (0.112)	<0.001	1.854 (1.488–2.310)
Family history of cardiovascular deaths*	0.40407 (0.086)	<0.001	1.498 (1.265–1.774)
GHb-A1c (increase of 1%)	0.24288 (0.044)	<0.001	1.275 (1.169–1.391)
Education level (1 = lower education, 2 = middle level education 3 = higher education)	−0.20389 (0.065)	0.002	0.816 (0.718–0.926)

Risk for cardiovascular event of individual risk factors in the Health 2000 study model expressed in one unit change (expressed in parentheses).
BP: blood pressure; CI: confidence limit; HDL: high density lipoprotein; MI: myocardial infarction; SE: standard error.
*Parental death from cardiovascular disease.

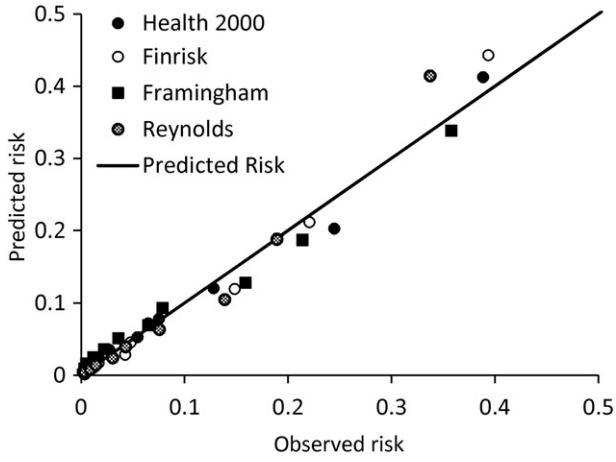

Figure 2. Plots for the Health 2000 and recalibrated Finrisk, Framingham and Reynolds risk scores.

Framingham ($\chi^2 = 26.5$, $p = 0.0008$) and Reynolds ($\chi^2 = 24.5$, $p = 0.002$) scores.

Model discrimination

The recalibrated estimated and observed risk predictions of the models are visualized in Figure 3. The *c*-statistic of the Health 2000 risk score (0.850) was significantly higher than for the recalibrated Framingham (0.829, $p < 0.001$ vs. Health 2000) and Reynolds risk scores (0.840, $p = 0.01$ vs. Health 2000), and almost reached statistical significance with the Finrisk score (0.845, $p = 0.055$ vs. Health 2000), (Table 3). Using the Health 2000 risk score instead of the Framingham score also resulted in a significant net reclassification index (21.7%, $p < 0.0001$, Table 3). The net reclassification indices for the differences between the Health 2000 model and the Finrisk or the Reynolds models were nonsignificant ($p \geq 0.71$ for both) although the integrated discrimination indices were significant ($p \leq 0.01$ for both).

We compared as well the Health 2000 risk score with and without the new covariables (ECG-LVH, GhBA1c and education level). The c-statistics, net reclassification index and integrated discrimination index of the Health 2000 risk score with the new covariables were significantly higher than without the new covariables (change in c-statistics: 0.006, $p = 0.003$, net reclassification index: 9.7, $p < 0.0001$, and integrated discrimination index: 4.5, $p < 0.0001$) (Table 3).

Internal validation of the Health 2000 cardiovascular risk score

The results of the internal validation using cross-validation and bootstrap resampling supported the stability of our model (Supplementary Table S1). In cross-validation, the degree of optimism was 0.003. In bootstrapping, no optimism was found.

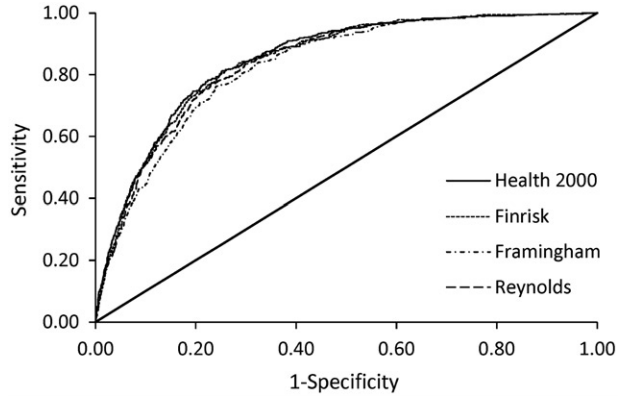

Figure 3. ROC curves for the Health 2000, Finrisk, Framingham and Reynolds risk scores.

Table 3. Comparison of models for cardiovascular events in the Health 2000 study based on survival estimates for recalibrated risk scores.

Model comparison	Change in c index	Category NRI, %	IDI, %
Health 2000 vs. Framingham	0.021	21.7	4.8
p	<0.0001	<0.0001	<0.0001
Health 2000 vs. Finrisk	0.004	0.73	−0.9
p	0.055	0.71	0.007
Health 2000 vs. Reynolds*	0.007	0.81	−1.2
p	0.011	0.73	0.002
Health 2000 vs. Health 2000 (reduced)**	0.006	9.7	4.5
p	0.003	<0.0001	<0.0001

Health 2000 risk score includes the following covariants: age, sex, systolic BP, total cholesterol, HDL cholesterol, smoking status, GHb-A1c, education level, ECG LVH (assessed using the Cornell volts) and family history of cardiovascular deaths. NRI: net reclassification improvement index; IDI: integrated discrimination improvement. The NRI categories were 5%, 10% and 20%.

*Comparison between Health 2000 and Reynolds risk scores doesn't include diabetics.

**without ECG-LVH, GhBA1c and education level.

Discussion

In this study, we constructed an improved cardiovascular risk prediction score for the Finnish population. The Health 2000 score improved cardiovascular risk prediction in the nationwide Finnish study population, compared with other traditional cardiovascular prediction scores the Finrisk, Reynolds and the Framingham scores (6,14,15).

The Health 2000 cardiovascular risk score appeared well calibrated. Adding new covariables (ECG-LVH, GhBA1c and education level) to the existing Health 2000 model significantly improved the risk prediction of the model. Recalibration of the Finrisk, Reynolds and the Framingham risk scores to correspond the average cardiovascular risk of the Health 2000 model did not

show any major difference compared with the original models. Internal validation of the Health 2000 study cohort showed good performance of our model (Supplementary Table S1).

The Framingham risk score was selected as one of the models that we used to validate our own because it is a widely used and is regarded as the golden standard for cardiovascular risk assessment (14). The Finrisk score was selected because it is the most widely used risk score in Finland and has been constructed using a population similar to the Health 2000 study. However, the Finrisk score does not include coronary interventions as an endpoint in contrast to our study. The number of coronary interventions, and especially percutaneous interventions have increased greatly in Finland since the 1990s and are now routinely performed in the health care units. This increase has in part modified the distribution and timing of endpoints by delaying possible coronary heart disease and myocardial infarctions to older age-groups. Furthermore, aggressive medical therapy is usually initiated after coronary interventions, which drastically alters the risk profiles of patients. We believe that including revascularizations as the endpoints provides more accurate results, and therefore more accurately reflects the current situation in Finland and other Western countries. The Reynolds risk score however includes revascularizations in the endpoints although it cannot be used in diabetic men, which our risk score allows. Furthermore, our risk score was superior to the Reynolds risk score in non-diabetics at predicting cardiovascular events.

Neither the Finrisk, Reynolds or the Framingham risk scores include ECG-LVH as a risk factor, whereas our risk score does. In fact, ECG-LVH was a highly significant covariate in our prediction models. We think that this is a major advantage because the ECG is widely used examination in the health care units, but not very often effectively utilized in cardiovascular risk prediction.

In previous studies it has been found that the family history of cardiovascular events, inflammation (hs-CRP) and GHb-A1C among diabetic subjects might improve the cardiovascular risk prediction (4,6,21,22). In our study we found that both family history of cardiovascular deaths (death of at least one parent for myocardial infarction or stroke) and GHb-A1C was more strongly associated with cardiovascular events than diagnosis of diabetes. We also examined the impact of hs-CRP as a risk factor, but it did not reach statistical significance.

In our study, we found that lower education level was strongly associated with a higher cardiovascular risk. In the QRISK study, cardiovascular risk was found to vary according to neighborhood, indicating that underlying social factors might explain this association (2). Education level as a cardiovascular risk factor is most likely a marker of underlying lifestyle factors affecting total cardiovascular risk, such as diet and exercise (23). However, these factors are very difficult to accurately quantify in an individual. Although there is wide inter-individual variation within education level groups, it seems that education level can be used as a rough estimate on the lifestyles of an individual.

Limitations of the study

We could not examine the validity of our cardiovascular risk prediction in ethnically diverse populations as has been done in some studies (2,4). The Health 2000 study was a nationwide study representing only the relatively homogenous Finnish adult general population. External validation using a similar population cohort and cardiovascular endpoints as in our study would have warranted a more extensive utilization of our risk score. External validation for our cardiovascular risk score might possibly be performed in the future. Instead, we performed internal validation using cross-validation with bootstrap resampling, which showed good stability of our cardiovascular risk score. Our study had a follow-up time of approximately 10 years, which is similar to other studies (2). However, the number of subjects in our study was relatively small compared to other studies (2). Furthermore, the limit of quantitation of hs-CRP in our study was 0.20mg/L. With a more sensitive analysis method it might have reached statistical significance.

Conclusions

In this study we assessed the cardiovascular risk in a nationwide Finnish population and found that the new Health 2000 score including the broadest range of available endpoints (including coronary revascularizations), improved the cardiovascular risk prediction in the current study population. We believe that our Health 2000 risk score would improve the ability to identify subjects at a high risk for developing cardiovascular disease in the Finnish and possibly also in other Caucasian populations.

Disclosure statement

None of the authors had a personal or financial conflict of interest.

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