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Lifetime risk predictions for cardiovascular diseases: Competing risks analyses on a population-based cohort in Sweden

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ABSTRACT

Background and aims: There are guideline discussions on a lifetime approach to cardiovascular risk. Many of the available risk models estimate the short-term, usually 10-year risk of non-fatal and fatal cardiovascular diseases (CVD) grouped together. We aimed to develop lifetime risk models for non-fatal coronary heart disease, stroke, heart failure and death from CVD and non-CVD.

Methods: We included 92,915 individuals who had participated in a community-based lifestyle intervention programme at 40, 50 and/or 60 years of age. Their collected data on selected risk factors were linked to register data on hospitalizations and death. Parametric multivariable survival regression with a competing risks approach was employed to model cause-specific hazards, which were translated into cumulative incidence functions to provide the risk of experiencing each event separately. All analyses were performed gender-age wise. For illustrative purposes, "better" and "worse" risk profiles were created by setting three modifiable risk factors to the best and worst levels, respectively.

Results: Most of the risk factors qualified for inclusion in the regressions. Men had a higher risk of cardiovascular events and the events occurred at a younger age than women. In the created risk profiles, where serum total cholesterol, smoking status and blood pressure were modified, an excessive number of CVD events were observed in the worse profiles.

Conclusions: Using these models, the lifetime risk of each of the first CVD events can be estimated for different risk factor profiles. Since the predictions are diagnosis specific, the estimates are more accurate.

1. Introduction

Cardiovascular diseases (CVDs) are the leading cause of death globally. In recent decades, cardiovascular mortality rates have been decreasing. However, because of ageing and growing populations, on a global level, the total number of deaths from CVDs has risen [1]. In Sweden, there has been a declining trend in cardiovascular mortality [2], but CVDs remain the number one cause of death, accounting for one third of all deaths [3]. CVD hospitalization rates are also declining [4] but CVDs are still the most common cause of inpatient care [5]. The most common CVDs are coronary heart disease (CHD), stroke and heart failure (HF) [2,4].

Atherosclerosis underlies most CVDs and is caused by a combination of risk factors. These risk factors are well established and include physical inactivity, smoking, unhealthy diet, harmful alcohol consumption, obesity, diabetes, abnormal lipids, hypertension and psychological factors. Factors such as gender, age, education and heredity also contribute to the risk [6–8]. Because of these multiple and combinatory causes of the pathological process of atherosclerosis, guidelines on the prevention of CVD [9] recommend an assessment of an individual's total CVD risk since an individual with multiple mildly raised risk factors may be at higher risk than an individual with only one, more pronouncedly elevated risk factor.

Risk models combine several risk factors for fatal and/or non-fatal events in a statistical model. For CVD, many risk models already exist. A number of models are derived from the well-known Framingham studies [10,11]. Other examples of established risk models also based on general population samples are SCORE [12] and the QRISK models [13–15].

However, most of the available risk models predict the risk of cardiovascular diagnoses grouped together (e.g. CVD overall) and/or non-

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fatal and fatal events combined. Thus, there is a scarcity of models for specific CVDs, and also for non-fatal and fatal events separately [16].

Moreover, many of the cardiovascular risk models available today estimate short-term (usually 10-year) risk [16]. However, a majority of middle-aged individuals with a low short-term risk are also at high long-term risk due to their risk factor burden [17]. The greatest number of CVD events occur in those individuals with low short-term risk since there are many more of them [18]. To balance this, guidelines [9] recommend using relative risk or cardiovascular risk age. Lifetime CVD risk assessment is brought up in the guidelines [9,19–21]. Although not yet recommended for treatment decisions, it serves as an illustration of risk and encouragement of a healthy lifestyle.

In an era of guideline discussions [19] and considerations [20,21] of a lifetime approach to CVD risk, we aimed to develop separate lifetime risk models for non-fatal CHD, stroke, HF and death from CVD and non-CVD.

2. Materials and methods

2.1. Study design

In our dynamic cohort study, we used data on risk factors from the Västerbotten Intervention Programme (VIP) linked to the nationwide Swedish Cause of Death and Inpatient Registers. The study population was followed from the date of participation in the VIP (1989–2014) until non-fatal events of interest, death or December 31, 2014, whichever occurred first. Ethical approval was granted by the Regional Ethical Board in Umeå, Sweden (diary numbers 2014-196-32 M and 08–131 M).

The VIP is a population-based countywide lifestyle intervention programme that aims to prevent premature CVD and diabetes [22]. The programme started as a pilot in one municipality in 1985 and was gradually expanded from 1989 to 1992 to include the entire county. Since 1995, it has been integrated into primary care procedures. Residents of Västerbotten County (total population 272,000 in 2019) in northern Sweden are invited to a health examination (risk factor screening) and individual health counselling when they reach 40, 50 and 60 years of age. The participants provide informed consent for future research. For the vast majority, the consent is written. In the VIP, height, weight, blood pressure, glucose tolerance and lipid measurements are taken. The participants also answer a comprehensive questionnaire covering socioeconomic and psychosocial conditions, self-rated health, medications, personal and family history of CVD and diabetes, quality of life and lifestyle habits. The health information retrieved serves as a basis for individual counselling by nurses on lifestyle modifications. Depending on risk factor levels, the participant may be referred to a general practitioner for further assessment and pharmacological treatment may be initiated according to clinical guidelines. More details about the programme have been provided elsewhere [22].

The Cause of Death Register includes all residents of Sweden and contains data on death and the underlying cause [23]. The Inpatient Register covers all inpatient care in Sweden and contains diagnoses and other data on hospital discharges [24].

2.2. Inclusion criteria

This study applied the following inclusion criteria: free of CVD and diabetes at participation in the VIP. Free of CVD was defined as follows: (i) no previous hospitalization due to CVD, and (ii) did not answer 'yes' to the question about having been hospitalized due to myocardial infarction. CVD was defined according to the International Classification of Diseases (ICD)-10 codes in Chapter I or ICD-8/9 codes 390–459 as primary diagnosis in the inpatient register. Free of diabetes required that the participant did not answer 'yes' to the question about having diabetes and did not fulfil the World Health Organization criteria of diabetes diagnosis (fasting plasma glucose $\geq$ 7.0 mmol/L or 2-h capillary plasma glucose $\geq$ 12.2 mmol/L) at participation in the VIP.

2.3. Variables

The non-fatal events provided by primary diagnosis in the Inpatient Register were defined as follows:

- CHD: ICD-10 codes I20–I25 or ICD-9 codes 410–414
- Stroke: ICD-10 codes I61, I63 or I64 or ICD-9 codes 431, 434 or 436
- HF: ICD-10 code I50 or ICD-9 code 428

If death (from any cause) occurred within 28 days of any of the non-fatal events, the event was recoded as CVD death, which was otherwise defined as death with the underlying cause being an ICD-10 code in Chapter I or ICD-9 codes 390–459.

The selection of candidate variables was based on traditional risk factors of CVD and variable completeness in the VIP. The selected variables were: dyslipidemia (serum total cholesterol), smoking, blood pressure, overweight/obesity (body mass index [BMI]), physical activity, self-rated health, education and marital status.

2.4. Statistical analysis

Survival analysis with a competing risks approach was employed to model the cause-specific hazards (CSHs) of the first of the CVD events or death. The study subjects were censored at the occurrence of any of the other non-fatal CVD events, death or December 31, 2014, whichever occurred first. The time scale was years, counted from the date of participation in the VIP. Parametric regression modelling was used, and the parametric models under consideration comprised three models in the proportional hazards metric: exponential, Weibull and Gompertz, and two models in the accelerated failure-time metric: lognormal and loglogistic. Model selection was based on Akaike's Information Criterion (AIC) and Bayesian Information Criterion (BIC).

The candidate variables were tested for inclusion in the regression models. Decisions on whether or not to categorize continuous variables were based on an assessment of the cause-specific hazard ratios (CSHRs) and the statistical significance of continuous format *versus* categories. The categories were mainly based on established clinical cut-offs. If an apparent trend was seen in CSHRs of different categories and was deemed not to have been captured in the continuous CSHR, and/or if the *p*-value decreased when the variable was categorized, then categorization was selected. Whether or not response alternatives were grouped into fewer categories was based on an assessment of the CSHRs of the original categories. Categories with similar CSHRs and which could be considered to be similar, e.g. 'quite poor' and 'poor', were grouped together. Details of the original format/response alternatives and the format/categories used in the analyses are shown in Table 1. In deciding which candidate variables to include in the multivariable regressions, univariable analyses of association were initially run and a significance level of 0.10 (for categorical variables: between any two of the categories) was applied as a decision rule.

As the data this study is based on have been collected over a time frame of 25 years, temporal changes may have taken place. In preliminary analyses, we noted some indications of time trends in the CSHRs. However, they were not monotonic and the level of variation was considered to be acceptable in relation to the increased power of analyses based on a larger dataset from the entire time frame.

The regressions were performed gender-age wise, i.e. men aged 60 years, women aged 60 years, men aged 50 years, etc. Thus, participants who had participated in the VIP more than once could be included in more than one of the age groups if they were still free of CVD and diabetes at their next participation. Only participants who had complete data on all the candidate variables were included. Analyses were not performed in the regression models that had less than the rule of thumb of 10 events per covariate.

For models in the proportional hazards metric, the assumption of proportional hazards was assessed using the scaled Schoenfeld Residuals

Table 1
Candidate variables.

	Original format/ response alternatives	Format in the analyses
Serum total cholesterol	Continuous	• <5.00 mmol/L • 5.00–7.49 mmol/L • ≥7.50 mmol/L
Smoking status	• Never smoker • Cigarette smoker • Cigar smoker • Pipe smoker • Occasional smoker • Former regular smoker • Former occasional smoker	• Never/former (regular or occasional)/occasional. • Frequent (cigarette, cigar or pipe)
Blood pressure	Continuous + question on the use of different classes of medicines in the previous 14 days (one of the response alternatives is antihypertensives)	• Optimal (systolic blood pressure <120 mmHg and diastolic blood pressure <80 mmHg and not on antihypertensives). • Pre-high (systolic blood pressure 120–139 mmHg or diastolic blood pressure 80–89 mmHg). • High (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or on antihypertensives)
BMI, kg/m^2	Continuous	Continuous
Physical activity	Response alternatives from three questions on physical activity (when commuting, during recreational activities and physical exercise, respectively)	• Sedentary • Moderately active • Physically active See Ng et al. [36] for details on category definitions
Self-rated health (previous year)	• Very good • Pretty good • Fairly good • Quite poor • Poor	• Very good • Pretty good • Fairly good/quite poor/poor
Education	Nine response alternatives for current and previous educational levels in Sweden	• Basic ("elementary school") • Middle ("upper secondary school") • High ("college/university")
Marital status	• Unmarried • Married/cohabiting • Widow/widower • Divorced • Remarried	• Married/cohabiting (married/ cohabiting/ remarried) • Single (unmarried/widow/ widower/divorced)

Test [25] of Cox models for each event and gender-age group, respectively. If the global test (full model) indicated significant violation of the PH assumption ($p < 0.05$), then each respective variable for which non-proportionality was suggested was further investigated.

The predictive performance of the regressions was assessed using Harrell's concordance [26] (c-statistic) as a measure of discrimination in the time period where the dataset had observed events.

2.5. From cause-specific hazards to risk prediction

The CSH of each event gives the instantaneous rate of failure from the event conditional on not having experienced any of the other competing events. As the interpretation of this is not straightforward, the CSHs, $h_k(t)$, were translated into cumulative incidence functions, $F_k(t)$, which provide the probability of experiencing each event, respectively, at time t.

$$F_k(t) = \int_0^t h_k(u) \cdot S(u) \cdot du$$

where the event-free survival S(t) that takes all the competing events into consideration is defined as:

$$S(t) = exp\left\{ -\sum_{k=1}^{K} H_k(t) \right\}$$

and the cumulative cause-specific hazard $H_k(t)$ is defined as:

$$H_k(t) = \int_0^t h_k(u) \cdot du$$

For illustrative purposes, we estimated the risks of the events by defining "better" and "worse" risk profiles and compared them to each other and also to the average of each gender-age group. The better and worse profiles were constructed by setting three modifiable risk factors with significant effect on the rate of events to the best/worst level, while the other variables were kept at each participant's observed value.

All statistical analyses were performed using STATA (version 15) in which the streg command was used to fit the parametric models and to automatically check for collinearity, the estat phtest and stphcoxrcs [27] commands were used to assess the proportional hazards assumption, the somersd [26] command was used to assess discrimination, and the standsurv [28] command was used for derivation of the cumulative incidence functions. Statistical significance was defined at the 0.05 level.

3. Results

3.1. Study population

A total of 92,915 participants, who had participated 127,401 times together in the VIP, were included in our study. The total time at risk ranged from 152,242 to 281,877 person-years in the respective gender-age groups in which the aggregate number of first events was 13,247 (5532 coronary heart disease, 2269 stroke, 518 heart failure, 3841 non-CVD death and 1087 CVD death) when events analysed in more than one of the groups were allowed to be counted again. Missing values in any of the candidate variables were present in 0.7–2.6% of the self-reported variables and 0.4–0.7% of the clinically measured variables. This resulted in the removal of 4.4–6.5% of the potentially eligible participants in the respective gender-age groups. The characteristics of the study population are presented in Table 2.

3.2. Model selection

Based on assessments of the AIC and BIC of the parametric models considered, the Gompertz distribution was selected for all analyses. In regressions with no covariates, this model showed the lowest AIC and BIC for all first events in all gender-age groups, except for the men aged 60, men aged 50 and women aged 40 groups for CHD, women aged 40 for HF and men aged 40 for CVD death, in which Weibull produced slightly lower AIC/BIC (data not shown). Gompertz was still selected based on the proximity of AIC/BIC values and that all other regressions indicated this distribution.

3.3. Validity of the proportional hazards assumption

The full model assessments for stroke, HF and CVD death suggested no violation of the proportional hazards assumption while, for the CHD models, violation was indicated in all Cox models, except for women aged 40 years. Violation was also indicated in some of the non-CVD

Table 2
Study population characteristics.

	Men 60 n=16,771 T=152,242	Women 60 n=19,724 T=198,260	Men 50 n=21,533 T=233,649	Women 50 n=23,624 T=271,831	Men 40 n=22,096 T=254,052	Women 40 n=23,653 T=281,877
Age [years], mean (SD)						
	60.0 (0.3)	60.0 (0.3)	50.1 (0.3)	50.0 (0.2)	40.1 (0.3)	40.1 (0.3)
Serum total cholesterol [mmol/L], n (%)						
<5.00	4169 (24.9)	3129 (15.9)	5735 (26.6)	7168 (30.3)	8542 (38.7)	13,068 (55.2)
5.00-7.49	11,825 (70.5)	14,923 (75.7)	14,724 (68.4)	15,636 (66.2)	12,883 (58.3)	10,366 (43.8)
≥7.50	777 (4.6)	1672 (8.5)	1074 (5.0)	820 (3.5)	671 (3.0)	219 (0.9)
Smoking status, n (%)						
Never/former/infrequent	14,340 (85.5)	16,720 (84.8)	18,148 (84.3)	19,345 (81.9)	19,608 (88.7)	20,239 (85.6)
Frequent	2431 (14.5)	3004 (15.2)	3385 (15.7)	4279 (18.1)	2488 (11.3)	3414 (14.4)
Blood pressure						
Optimal	2002 (11.9)	3380 (17.1)	4502 (20.9)	8007 (33.9)	6690 (30.3)	13,006 (55.0)
Pre-high	6710 (40.0)	7986 (40.5)	10,170 (47.2)	9970 (42.2)	11,535 (52.2)	8544 (36.1)
High	8059 (48.1)	8358 (42.4)	6861 (31.9)	5647 (23.9)	3871 (17.5)	2103 (8.9)
BMI [kg/m^2], mean (SD)						
	26.5 (3.4)	26.2 (4.3)	26.5 (3.6)	25.6 (4.4)	26.3 (3.8)	25.0 (4.6)
Physical activity, n (%)						
Sedentary	3345 (19.9)	2214 (11.2)	4701 (21.8)	2683 (11.4)	4863 (22.0)	2805 (11.9)
Moderately active	10,217 (60.9)	13,840 (70.2)	12,199 (56.7)	15,359 (65.0)	11,780 (53.3)	14,436 (61.0)
Physically active	3209 (19.1)	3670 (18.6)	4633 (21.5)	5582 (23.6)	5453 (24.7)	6412 (27.1)
Self-rated health, n (%)						
Very good	4865 (29.0)	4582 (23.2)	6462 (30.0)	6440 (27.3)	6348 (28.7)	6663 (28.2)
Pretty good	7730 (46.1)	8879 (45.0)	10,327 (48.0)	10,722 (45.4)	11,005 (49.8)	11,089 (46.9)
Fairly good/ quite poor/poor	4176 (24.9)	6263 (31.8)	4744 (22.0)	6462 (27.4)	4743 (21.5)	5901 (24.9)
Level of education, n (%)						
Basic	5963 (35.6)	6814 (34.5)	4350 (20.2)	4350 (18.4)	2215 (10.0)	2001 (8.5)
Middle	7332 (43.7)	7652 (38.8)	11,791 (54.8)	10,871 (46.0)	13,519 (61.2)	11,992 (50.7)
High	3476 (20.7)	5258 (26.7)	5392 (25.0)	8403 (35.6)	6362 (28.8)	9660 (40.8)
Marital status, n (%)						
Married/cohabiting	13,775 (82.1)	15,449 (78.3)	17,351 (80.6)	19,255 (81.5)	17,646 (79.9)	19,885 (84.1)
Single	2996 (17.9)	4275 (21.7)	4182 (19.4)	4369 (18.5)	4450 (20.1)	3768 (15.9)
First event, n (%)						
CHD	1723 (10.3)	894 (4.5)	1481 (6.9)	571 (2.4)	656 (3.0)	207 (0.9)
Stroke	639 (3.8)	578 (2.9)	482 (2.2)	275 (1.2)	181 (0.8)	114 (0.5)
HF	181 (1.1)	111 (0.6)	101 (0.5)	61 (0.3)	44 (0.2)	20 (0.1)
Non-CVD death	1030 (6.1)	1053 (5.3)	639 (3.0)	623 (2.6)	262 (1.2)	234 (1.0)
CVD death	406 (2.4)	241 (1.2)	240 (1.1)	84 (0.4)	79 (0.4)	37 (0.2)
Censored	12,792 (76.3)	16,847 (85.4)	18,590 (86.3)	22,010 (93.2)	20,874 (94.5)	23,041 (97.4)

n, number, T, total time at risk (person-years), SD, standard deviation BMI, body mass index, CHD, coronary heart disease, HF, heart failure, CVD, cardiovascular disease.
Note: The total number of VIP participants included in this study does not equal the sum of the numbers above as the participants may have been be included in more than one of the age groups.

death models (data not shown). The assessments of the individual covariates in which non-proportionality was suggested showed that there were mostly decreasing trends over time, i.e. higher CSHRs in earlier years than in later years, compared to the time-fixed CSHRs. The non-proportionalities were mainly noted in being a frequent smoker and in the worst categories of self-rated health and serum total cholesterol. However, a decision was made to keep the covariates in the models without adjustments, with interpretations of these estimates as average effects.

3.4. Parametric regressions

The adjusted CSHRs of the multivariable Gompertz regressions for each of the first events, respectively, are listed in Table 3. The 95% confidence intervals of the CSHRs are presented in Supplementary Table 1. Due to few first events of HF and CVD death in both age 40 groups, adjusted CSHRs are missing for these regressions. The unadjusted CSHRs of the univariable regressions are shown in Supplementary Table 2.

Trends in the adjusted CSHRs were generally similar for the respective events and in the respective gender-age groups. However, serum total cholesterol ≥7.50 mmol/L showed contrasting results between the events. The CSHRs increased the rate of CHD more markedly than stroke in particular, but also CVD death, and for HF, it decreased the rate. Frequent smoking was included in most of the regressions and the adjusted CSHRs remained significant, with the highest CSHRs noted for CVD death, particularly for women. Among the categorical variables, high blood pressure and frequent smoking increased the rates of events the most and the CSHRs of high blood pressure were generally higher in women than men. While BMI did not remain statistically significant in most of the multivariable regressions, it remained significant in all HF regressions, in which it increased the rate. Physical activity indicated increasing rates of events with a sedentary lifestyle and decreasing rates of events with a physically active lifestyle in most regressions. Assessing self-rated health as fairly good, quite poor or poor increased the rates of events compared to very good. For level of education, the trend was similar to physical activity, with the CSHRs of high level of education decreasing the rates of events and basic level of education increasing the rates of events in most regressions. Single status had no apparent association with the rates of CHD, while the CSHRs increased the rate of most of the other first events.

The discrimination measured by c-statistics ranged from 0.60 to 0.78. Discrimination was generally best for CVD death (data not shown).

3.5. Risk predictions

The CSHs were translated into the cumulative incidence functions presented in Fig. 1, which reflect the average for our study population. Due to missing CSHs of some of the events, no cumulative incidence functions were estimated in the age 40 groups. We noted gender differences: men had higher risks of a first CVD event and experienced CVD

Table 3
Cause-specific hazard ratios (CSHRs) from multivariable Gompertz regressions.

Variable (reference level)		Cholesterol, mmol/L (<5.00)		Smoking status (never/ former/ infrequent)	Blood pressure (optimal)		BMI, kg/m^2	Physical activity (moderately active)		Self-rated health (very good)		Level of education (middle)		Marital status (married/ cohabiting)	Constant	Gamma
		5-7.49	≥7.50	Frequent	Pre-high	High		Sedentary	Physically active	Pretty good	Fairly good/ Quite poor/ Poor	Basic	High	Single		
Men 60	CHD	1.316***	2.013***	1.332***	1.276**	1.655***		1.021	0.959	1.250***	1.454***	1.075	1.022		-5.599	0.031
	Stroke	1.121	1.373	1.566***	1.252	1.810***	1.011	1.092	0.804	1.288*	1.334*	1.028	0.911	1.327**	-7.205	0.080
	HF			2.339***	1.188	1.836*	1.056**	0.848	0.745	0.967	1.396	1.008	0.649	1.240	-9.733	0.116
	Non-CVD death			1.919***			0.985	1.052	0.921	1.109	1.248**	1.183*	1.019	1.216*	-6.007	0.123
	CVD death	1.228	1.110	2.364***	1.048	1.442*	1.048***			1.174	1.484**	1.228	0.694*	1.713***	-8.992	0.109
Women 60	CHD	1.208	1.634***	1.620***	1.793***	2.692***	0.992	1.008	0.894	1.566***	2.072***	1.193*	0.769*		-7.114	0.049
	Stroke			1.383**	1.304	2.216***	1.000	1.094	0.777	0.938	1.176	1.231*	1.102	1.174	-7.547	0.110
	HF	0.516**	0.584	1.745*	1.731	2.759*	1.055**	1.624	1.177					1.475	-10.975	0.160
	Non-CVD death			1.895***				1.245*	1.057	1.147	1.427***	1.105	0.705***	1.195*	-6.745	0.124
	CVD death	0.865	1.317	3.343***	1.177	2.194***		1.085	0.602*	1.128	1.330	1.213	0.715	1.227	-9.081	0.150
Men 50	CHD	1.871***	2.972***	1.704***	1.247**	1.660***	1.025**	1.065	0.923	1.079	1.177*	1.195**	1.018		-7.273	0.058
	Stroke	0.977	1.479*	1.265*	1.182	1.771***	1.006	1.120	0.714*	1.135	1.554***	1.186	0.846	1.204	-7.729	0.092
	HF				2.083	4.121***	1.071**			1.429	1.913*	1.011	0.612	2.169***	-12.133	0.124
	Non-CVD death			2.295***	0.946	1.227		1.131	0.911	1.108	1.350**	1.100	0.893	1.413***	-7.410	0.111
	CVD death	1.285	2.581***	2.302***	1.471	2.470***	1.044*	0.867	0.802	1.500*	1.550*	1.422*	0.678	1.494**	-10.187	0.085
Women 50	CHD	1.456***	2.232***	1.844***	2.264***	3.286***	0.999	1.237	1.019	1.477**	1.890***	1.226*	0.843		-8.265	0.051
	Stroke	1.106	1.358		1.217	2.158***		1.279	0.840	0.989	1.338	1.125	1.002	1.322	-8.291	0.086
	HF	0.533*	0.161		0.704	2.035*	1.065**					0.990	0.510	2.151**	-11.026	0.129
	Non-CVD death			1.939***	0.853	1.120		1.158	1.004	1.074	1.397**	1.222*	0.857	1.178	-7.468	0.107
	CVD death	0.822	1.657	4.193***	1.433	3.560***		1.392	1.304	1.670	2.161*	1.177	0.603		-10.768	0.113
Men 40	CHD	1.945***	4.122***	1.889***	1.389**	2.123***	1.040***	1.119	0.865	1.065	1.330**	1.318**	1.118		-9.184	0.101
	Stroke	0.746	1.171	1.362	1.646*	2.599***	1.022			0.969	1.263	1.032	0.650*		-9.393	0.123
	HF															
	Non-CVD death			1.633***	1.251	1.691**	1.043**	1.090	0.819	1.006	1.503*	1.476*	1.102	1.889***	-9.674	0.104
	CVD death															
Women 40	CHD	1.834***	4.210***	2.001***	2.057***	3.499***	1.024			1.918**	2.250***	1.778**	1.081		-10.458	0.088
	Stroke	0.934	1.977	1.545*	1.376	2.027*	1.041*			0.974	1.303				-9.732	0.060
	HF															
	Non-CVD death			1.684***						1.166	1.855***	1.499*	1.010	1.162	-8.659	0.108
	CVD death															

BMI, body mass index, CHD, coronary heart disease, HF, heart failure, CVD, cardiovascular disease
*p<0.05, **p<0.01, ***p<0.001 (applies to the CSHRs)
Note: The cause-specific hazard (CSH) of a Gompertz model is given by $h_k(t|x_j) = \exp(\gamma t)\cdot\exp(\beta_0 + x_j\beta_x)$ where $\beta_x = \ln(CSHR_x)$. The 95% confidence intervals of the CSHRs are listed in Supplementary Table 1.

events at younger ages than women. In a lifetime perspective, the most common CVD event in our study population was CHD for men and stroke for women.

As worked examples, the predicted risks of "better" and "worse" profiles were estimated, see Supplementary Fig. 1, which also includes the average of each gender-age group. The better and worse profiles were set to the best and worst categories of serum total cholesterol, smoking status and blood pressure, respectively. The estimated 10-year and lifetime risks of these profiles are shown in Table 4. These can be translated into the number of excess CVD events (non-fatal CHD, stroke and HF + fatal CVD) for the worse profile, which for women aged 50 years, for example, is 6 per 100 compared to the average profile and 8 per 100 compared to the better profile, respectively, at 10 years. In a lifetime perspective, the corresponding numbers are 24 and 32 per 100, respectively.

4. Discussion

In this paper, we present lifetime risk models of the most common non-fatal CVD events, together with the risks of CVD and non-CVD deaths, respectively. It is evident that there are risk factor profiles in which a low 10-year risk still translates into a moderate, or even high, lifetime risk. The exemplified "worse" profile of women aged 50 years has an estimated 10-year risk of <10% for the four CVD events together, despite the lifetime risk being estimated at 65%.

To our knowledge, a Dutch study [29] based on data collected within the time frame of our study is the most similar study on lifetime risks of CVD. That study also took a competing risks approach and the same specific CVDs were considered, without distinction between non-fatal and fatal events, together with other CVD deaths and non-CVD deaths. For men aged 55, the total lifetime risk of CVD was 67.1%, which is generally comparable to our corresponding lifetime risks at 63.5% (men aged 50 years) and 59.1% (men aged 60 years). Women were found to have similar lifetime risks of CVD. This is contrary to our study in which women have a lower lifetime risk of CVD. Like our study, CHD was the first CVD event with the highest lifetime risk in men while in women it was cerebrovascular disease. Individuals with diabetes mellitus were included in the Dutch study, which may explain some of the differing results, besides the differences in definitions and baseline characteristics of the study populations.

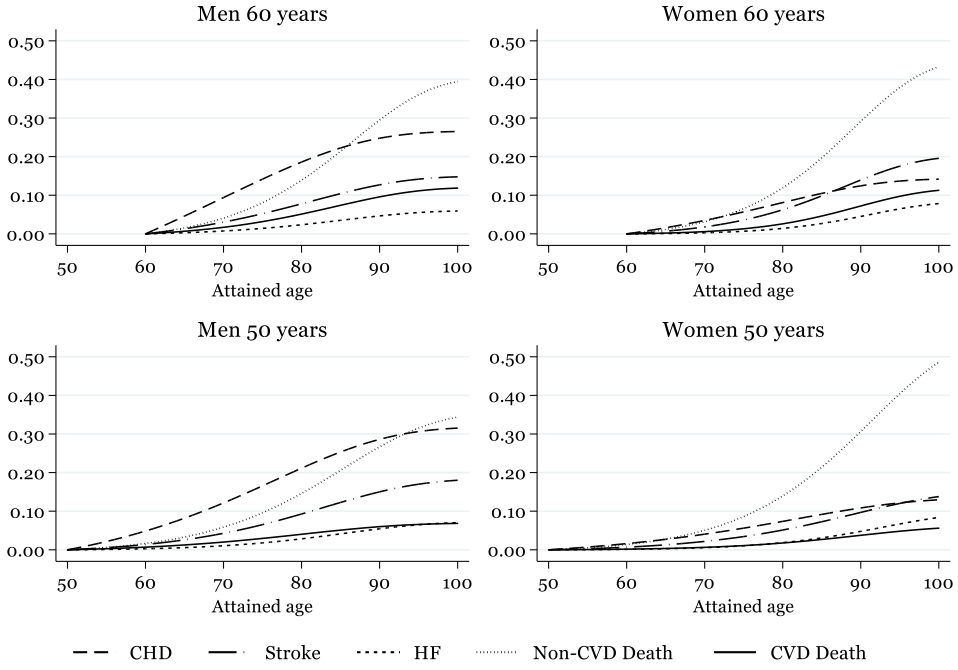
4.1. Implications

The focus on the first event is in alignment with the ultimate goal of primary prevention. By predicting the lifetime risk rather than the short-term (10-year) risk, more individuals will be considered for intervention as a result of the increased risks in a long-term perspective. If the short-term risk is still relatively low, these interventions may not comprise pharmacological treatments but will instead comprise lifestyle modifications, which could be initiated and motivated by the awareness of a relatively higher lifetime risk. CVD prevention guidelines [9] regard the lifetime approach as being important, although it is not yet recommended for treatment decisions. The usefulness of lifetime risk estimations is particularly endorsed in risk communication to individuals with low short-term absolute risks but with high aggregated risk factor levels. The guidelines also place greater emphasis on disease-specific interventions and on a population-based approach. By combining interventions that encourage a healthier lifestyle for a wider population (more numerous) with interventions aimed at individuals at high CVD risk (less numerous), reductions in CVD risk factors and, in turn, the occurrence of CVD at the population level would be possible.

The distinction between specific CVD diagnoses and whether or not events that have not yet occurred are non-fatal or fatal may not be relevant to the choice of preventive strategy. However, for healthcare resource and budgetary planning purposes, there are important implications in terms of, for example, length of stays, staff and equipment required, as well as the need for post-event care. Also, for health economic evaluations, this granularity enhances the quality.

4.2. Methodological considerations

This study is based on a large countywide dataset collected over 25 years. The VIP participation rates are high. Over time, they have increased to around 65% of invitees [30]. It has been concluded that the social selection bias in the VIP is small [30,31] and by applying the same manual, equipment and definitions/criteria in all centres, the VIP seeks



CHD, coronary heart disease, HF, heart failure, CVD, cardiovascular disease

Fig. 1. Average cause-specific cumulative incidences.

Table 4
Worked examples: 10-year and lifetime risks of first events (95% confidence interval), %.

		CHD		Stroke		HF		Non-CVD death		CVD death	
		10-year	Lifetime	10-year	Lifetime	10-year	Lifetime	10-year	Lifetime	10-year	Lifetime
Men 60	Better	5.17 (4.27-6.25)	17.45 (14.34-21.23)	1.79 (1.29-2.47)	11.53 (8.13-16.34)	0.44 (0.25-0.78)	5.25 (2.76-9.99)	3.77 (3.46-4.10)	52.11 (46.33-58.60)	1.03 (0.69-1.53)	10.57 (6.88-16.24)
	Average	9.40 (8.95-9.88)	26.52 (24.57-28.62)	3.04 (2.78-3.33)	14.78 (12.70-17.20)	0.74 (0.62-0.89)	5.92 (4.30-8.16)	4.09 (3.79-4.41)	39.46 (35.93-43.34)	1.69 (1.50-1.91)	11.86 (9.70-14.50)
	Worse	19.73 (16.66-23.37)	39.14 (33.85-45.26)	5.89 (4.29-8.08)	16.51 (12.34-22.09)	1.58 (1.13-2.20)	6.21 (4.34-8.89)	6.07 (5.32-6.93)	26.43 (22.39-31.20)	3.25 (2.15-4.92)	11.69 (7.99-17.08)
Women 60	Better	1.30 (0.95-1.78)	6.50 (4.63-9.11)	1.06 (0.80-1.42)	15.62 (11.23-21.73)	0.21 (0.09-0.49)	8.92 (3.54-22.50)	2.81 (2.57-3.07)	52.77 (45.70-60.94)	0.29 (0.17-0.51)	9.51 (5.12-17.66)
	Average	3.48 (3.23-3.76)	14.17 (12.49-16.07)	1.80 (1.62-2.01)	19.57 (16.25-23.57)	0.28 (0.22-0.37)	7.85 (4.88-12.61)	3.15 (2.91-3.41)	43.29 (38.62-48.51)	0.58 (0.48-0.70)	11.28 (8.27-15.37)
	Worse	8.55 (6.94-10.53)	23.77 (19.54-28.92)	3.00 (2.41-3.72)	16.37 (12.87-20.83)	0.54 (0.28-1.06)	5.99 (3.15-11.36)	4.88 (4.29-5.55)	30.87 (26.12-36.48)	2.58 (1.76-3.77)	22.96 (16.87-31.26)
Men 50	Better	1.97 (1.64-2.37)	18.31 (14.38-23.33)	1.00 (0.75-1.34)	20.33 (13.77-30.01)	0.11 (0.05-0.23)	5.03 (1.79-14.16)	1.33 (1.09-1.62)	46.63 (37.20-58.46)	0.26 (0.16-0.43)	4.40 (2.30-8.44)
	Average	4.86 (4.58-5.16)	31.53 (27.74-35.85)	1.38 (1.23-1.55)	18.02 (13.84-23.46)	0.27 (0.21-0.35)	7.05 (3.74-13.28)	1.65 (1.49-1.83)	34.35 (28.37-41.60)	0.69 (0.59-0.81)	6.85 (4.75-9.87)
	Worse	14.75 (12.44-17.48)	48.00 (42.01-54.84)	2.93 (2.08-4.12)	13.89 (10.02-19.26)	0.38 (0.27-0.52)	2.73 (1.74-4.27)	3.30 (2.73-3.99)	21.03 (16.90-26.18)	3.38 (2.26-5.04)	14.34 (9.87-20.83)
Women 50	Better	0.49 (0.36-0.65)	4.73 (3.17-7.07)	0.46 (0.33-0.65)	11.21 (6.46-19.46)	0.17 (0.09-0.33)	14.40 (4.83-42.93)	1.21 (1.02-1.43)	53.52 (41.32-69.31)	0.06 (0.03-0.12)	3.27 (1.07-10.00)
	Average	1.61 (1.45-1.78)	12.96 (10.10-16.62)	0.68 (0.58-0.80)	13.79 (9.02-21.09)	0.13 (0.09-0.18)	8.38 (3.18-22.12)	1.37 (1.23-1.52)	48.60 (39.18-60.29)	0.17 (0.12-0.23)	5.60 (2.52-12.47)
	Worse	6.24 (4.59-8.48)	30.22 (22.35-40.84)	1.29 (0.79-2.09)	11.76 (6.89-20.07)	0.05 (0.01-0.40)	1.19 (0.15-9.53)	2.48 (2.01-3.05)	34.55 (25.14-47.47)	1.46 (0.71-2.98)	22.00 (11.25-43.05)

CHD, coronary heart disease, HF, heart failure, CVD, cardiovascular disease.
Note: Lifetime = attained age 100 years. In the better profiles serum total cholesterol was set to <5.00 mmol/L, smoking status to never/former/infrequent and blood pressure to optimal. In the worse profiles serum total cholesterol was set to ≥7.50 mmol/L, smoking status to regular and blood pressure to high. The other variables were kept at the observed value of each participant. Average reflects the average of each individual's predicted risk based on observed values.

to minimize misclassification bias. The VIP data were linked to high-quality national registers with virtually complete coverage [23,24]. Participants with missing values in any of the risk factors accounted for a small proportion of the available data and their exclusion was assumed not to considerably impact the results.

With all analyses conducted gender-age wise, the potential for confounding from these two factors is diminished. Level of education is also known to be a potential confounder of health and we therefore controlled for it in our analyses.

Temporal changes may have taken place during the long period of data collection. These changes relate to the characteristics of the participants as well as trends and availability of treatment options for the diagnoses included here. The incidence and mortality of myocardial infarction and stroke have decreased, which has also been noted in the case of fatality for myocardial infarction [32], while for stroke it has been stable [33]. As new and more effective treatment options become available over time, the potential for preventing CVD events increases. The overall educational level of the population has increased over time, which also changes the general perception of what constitutes a basic level of education and a high level of education. However, in the methods section, we provide our rationale for making no adjustments for potential time trends.

There were some variables in which violation of the proportional hazards assumption was indicated. Among the modifiable risk factors, this was mainly an issue in the worst categories of smoking status and serum total cholesterol. As the VIP manual dictates the measures to be taken or even follow-up/referral of participants with bad values on clinical measurements or unfavourable lifestyles, this could influence the CSHRs downwards over time, which was generally noted. As no time adjustments were made, these CSHRs reflect the average effects.

Our dataset lacked information on emigration, meaning we could not censor observations at the time of emigration. This is not likely to affect the estimates much as we expect very few individuals in the study population to have emigrated.

In this study, all non-fatal events were based on hospitalization with any of the included diagnoses as primary diagnosis and where death did not occur within 28 days of hospital admission. It is unlikely that non-fatal CHD and stroke events will not result in hospital admissions, although HF could prevail without requiring inpatient care. Hence, it is likely that the incidence of HF has been underestimated in our results. In addition, as a large proportion of HF is attributable to CHD [34,35], focus on the first event, in any case, assumed that HF would be quite uncommon. However, although less frequent than CHD and stroke, HF is a common CVD diagnosis in terms of the total number of events in both hospitalization and cause-of-death measures, which was our justification for its inclusion.

Since no external validation of the risk models has been made to date, their performance outside of this study is unknown.

4.3. Conclusions

Using these models, the lifetime risk of each of the first CVD events can be estimated for different risk factor profiles. Since the predictions are diagnosis specific, the estimates are more accurate.

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CRediT authorship contribution statement

Anna Stenling: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Writing - original draft, Writing - review & editing. **Christel Häggström:** Methodology, Writing - review & editing. **Margareta Norberg:** Supervision, Writing - review & editing. **Fredrik Norström:** Conceptualization, Methodology, Supervision, Writing - review & editing.

Declaration of competing interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2020.08.014.

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