

# Although Coronary Mortality Has Decreased, Rates of Cardiovascular Disease Remain High: 21 Years of Follow-Up Comparing Cohorts of Men Born in 1913 With Men Born in 1943

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**Background**—Despite a decline in mortality rates from cardiovascular disease (CVD) in the past few decades, the burden of CVD in a contemporary population remains inadequately addressed. Therefore, this study was aimed to investigate secular trends in mortality from coronary artery disease and all-cause mortality over 2 decades, by comparing 2 cohorts of men born 30 years apart and evaluate the prediction of the risk of CVD and all-cause death in a contemporary random sample of Swedish men.

**Methods and Results**—Two cohorts of randomly selected men born in 1913 (855 men) and 1943 (798 men) were first examined at age 50 in 1963 and 1993, respectively, and followed longitudinally over 21 years. All-cause mortality and coronary artery disease death were lower in 50- to 71-year-old men born in 1943 compared with those born in 1913, with unadjusted hazard ratios of 0.57 (0.45–0.71) and 0.34 (0.22–0.53), respectively. After adjustment for risk factors (smoking, serum cholesterol, hypertension, systolic blood pressure, diabetes mellitus, body mass index, and physical activity), the differences between the cohorts remained significant for coronary artery disease, hazard ratios 0.57 (0.34–0.94),  $P=0.029$ , but not for all-cause mortality hazard ratios 0.82 (0.62–1.07),  $P=0.14$ . However, the rate of CVD events during follow-up was still high (30.7%) for the men born in 1943. No statistically significant interaction by birth cohort in contribution of risk factors to death was found between 2 cohorts except physical inactivity.

**Conclusions**—Despite a marked reduction in the rate of coronary artery disease death over the past 30 years, the burden of CVD events and all-cause mortality remains high. Therefore, intensified efforts to modify contributing risk factors are still required. (*J Am Heart Assoc.* 2018;7:e008769. DOI: 10.1161/JAHA.118.008769.)

**Key Words:** cardiovascular disease • death • longitudinal cohort study • population studies • risk factor

Despite a decline in mortality rates from cardiovascular disease (CVD) in the past few decades,<sup>1–3</sup> mostly attributable to improvements in known cardiovascular risk factors including smoking, hypertension, and hyperlipidemia,

as well as improved treatment modalities,<sup>4–7</sup> the cumulative burden of CVD in a contemporary population remains inadequately addressed. This is a relevant issue as CVD may take a longer time to develop, particularly in the light of improved primary cardiovascular prevention and simultaneously increased competing risk because of aging.

“The Study of Men Born in 1943” is a new longitudinal cohort study, the fourth of 6 studies of 50-year-old adults in Gothenburg, Sweden,<sup>8,9</sup> which started in 1963 with “The Study of Men Born in 1913.” These studies aim to investigate the prevalence of risk factors for CVD in consecutive samples of 50-year-old men recruited from the general population.<sup>8,9</sup> At 10-year intervals, new samples of 50-year-old men, living in the same urban area, have been investigated using the same methodology. Recently, we reported that the total cardiovascular risk factor burden in 50-year-old men had significantly decreased over the past 50 years.<sup>10</sup> A natural question arising from this observation was to ask whether the risk of all-cause mortality and coronary artery disease (CAD) mortality rates remains high and whether the contributions of risk

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## Clinical Perspective

### What Is New?

- Despite a decline in mortality rates from cardiovascular disease (CVD) in the past few decades, the burden of CVD in a contemporary population remains inadequately addressed.
- We investigated secular trends in mortality from coronary artery disease and all-cause mortality over 2 decades by comparing 2 cohorts of men born 30 years apart.
- We evaluated the risk factors of CVD and death in a contemporary random sample of Swedish men.
- Despite a marked reduction in the rate of coronary artery disease death over the past 30 years, the burden of CVD events and all-cause mortality remains high.

### What Are the Clinical Implications?

- Since the burden of CVD events and all-cause mortality remains high, intensified efforts to modify contributing risk factors are still required.
- Both CVD- and non-CVD-related death share many of the same risk factors.
- It is time to focus more on global than on disease-specific risk factors.

factors to these events have changed. To answer these questions, the present study sought to compare death from CAD and all-cause mortality in 2 random cohorts of men born 30 years apart from the general population in the same geographical area that were followed from 50 to 71 years of age, and to provide information on the total burden of CVD in the most recent cohort.

## Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request and ethical approval.

## Study Population

In 1963, a sample was drawn from the population register consisting of all men born in 1913 (cohort 1913) on a day divisible by 3 (eg, the third, the sixth, and ninth day of each month) and living in the city of Gothenburg. These criteria were fulfilled by 973 men out of whom 855 (87.9%) agreed to participate.<sup>8,9</sup> In 1993, the local tax authority in Gothenburg, Sweden generated a random sample of 50% of all men who were born in 1943 (cohort 1943) and were resident in the city of Gothenburg, and these men were invited to a health examination. Of 1463 invited men, 798 (54.5%) agreed to participate. In the cohort of men born in 1913, only 5% were

born outside of Sweden, while in the cohort of men born in 1943, 17% were born in another country. Informed consent was obtained from all participants. Except for the screening examination in 1963 where only oral informed consent was given, the study complied with the Declaration of Helsinki (which was established in 1964). The study protocol was approved by the Ethics Committee of Gothenburg University (DNR 157-93, 0067-03 and DNR 649-13).

## Follow-Up

Both cohort 1913 and cohort 1943 were followed for 21 years from age 50 years. In the cohort of men born in 1943, all surviving men underwent follow-up examinations in 2003 at age 60 years, when 655 out of 773 who were still alive (84.7%) took part in a re-examination, and in 2014, at the age of 71 years when 536 out of 688 men (77.9%) were examined. The cohort of men born in 1913 were re-examined at the age of 54, 60, and 67 years.

## Structured Interview

In both cohorts, and at each re-examination the same structured interview was conducted. Data on smoking habits, leisure time physical activity, previous diseases, and pharmacological treatment were collected. Leisure time physical activity was assessed by the Saltin–Grimby questionnaire<sup>11</sup> and coded as: 1=sedentary (physically inactive); 2=some light physical activity such as walking, riding a bicycle, or light gardening for at least 4 hours per week; 3=regular, moderate physical activity for a minimum of 3 hours per week; and 4=regular, vigorous physical training. Men who were current smokers or had quit smoking <1 month before the examination were categorized as smokers. Former smokers were defined as those who had quit smoking ≥1 month previously and never-smokers as those who had never used cigarettes, cigars, or a pipe on a regular basis.

## Clinical Examinations

Height and weight (in light indoor clothing) were measured and body mass index (weight in kg/[height in m]<sup>2</sup>) was calculated. A standard cuff and a mercury manometer were used to measure blood pressure. Hypertension was diagnosed based on either medical history with current antihypertensive therapy or current blood pressure ≥140 (systolic), ≥90 mm Hg (diastolic), or both. Fasting blood or plasma glucose, serum cholesterol, and triglyceride measurements were determined at the local accredited laboratory. Hyperlipidemia was defined as total cholesterol >6.2 mmol/L (1913 and 1943 cohort) or using lipid-lowering medication (1943 cohort). Diabetes mellitus was defined as fasting

plasma glucose  $>7$  mmol/L (1913 and 1943 cohort) or using oral medication and/or insulin (1943 cohort). A standard 12-lead ECG was recorded. Overweight was defined as body mass index  $\geq 25$  kg/m<sup>2</sup> (1913 and 1943 cohort) or waist  $>94$  cm (1943 cohort).

### Definition of CVD Risk Factors in the 2 Cohorts

Number of CVD risk factors was defined as the sum of overweight/obese, hypertension, being a smoker, diabetes mellitus, hyperlipidemia, and sedentary leisure time.

### Event Identification

The ascertainment of overall death and of CAD death was identical in the 2 cohorts, with no loss of follow-up, by access to the Swedish Cause-Specific Death Register in operation since 1964. CAD death was defined by the *International Classification of Diseases (ICD)* codes 420 (*ICD 7*), 410 to 414 (*ICD 8–9*), and I20 to I25 (*ICD 10*). Autopsy rates have decreased but are mandatory in cases of out-of-hospital deaths when there is no apparent cause of death (eg, in sudden death without prior history of coronary heart disease).

For the men born in 1943, the occurrence of cardiovascular events during follow-up was determined by a combination of 3 procedures: data from the Swedish National Health Registry, a review of medical records, and the screening examinations. The Swedish National Inpatient Register and the Swedish Cause of Death Register include all inpatient care and deaths in Sweden. Medical records of the men who reported having CVD at the 2 follow-up examinations were studied to verify any diagnoses during follow-up. Heart failure was defined as being hospitalized for heart failure (I50), heart failure reported on a death certificate, a history of heart failure identified at examination and verified in medical records, or heart failure newly diagnosed at the final examination in 2014 based on symptoms and echocardiography and according to current heart failure guidelines.<sup>12</sup> The occurrence of atrial fibrillation (AF) during follow-up was defined as a history of AF verified by medical records, AF identified on ECG at any of the examinations, or AF newly detected at the final examination supplemented with thumb ECG for 2 weeks. The criteria for defining a CVD event were the time to first occurrence of myocardial infarction, heart failure, AF, stroke, intermittent claudication, CAD death, and revascularization procedures.<sup>13</sup> In addition, CVD death was defined according to the Systematic Coronary Risk Evaluation (SCORE).<sup>14</sup> All end points were reviewed by 1 of 5 physicians. A history of CAD without hospitalization or revascularization was not considered to meet the definition of CVD.

### Statistical Analysis

For the baseline characteristics of participants, continuous variables were described by mean and SD, while categorical variables were reported as frequencies (%). The follow-up time was described by median and interquartile range. Crude incidence rates were expressed as event rates, calculated as the number of events divided by the sum of follow-up years per 1000 person-years, with exact 95% Poisson confidence limits. Kaplan–Meier curves were calculated for time to first CVD event and death. From these curves, 10- and 20-year survival rates were estimated with 95% confidence limits. Univariable and multivariable, using stepwise regression, Cox regression analyses were performed for prediction of CVD or death using the variables collected at baseline as possible predictors. The effect of continuous predictors on outcome was examined both as linear and piecewise linear functions with a median break point. The best model fit, defined by the lowest Akaike's information criterion, was then selected for each continuous variable. Updated analyses were also applied to evaluate catch-up effects of risk factors measured at different examinations and based on the time points and proportion of examined patients that were still alive at the 2 subsequent re-examinations from baseline. The assumption of proportional hazards was examined by introducing to the model an interaction term with time. This assumption was found to be satisfactory for all significant predictors of time to first CVD event. For time to death, the assumption also proved to be satisfactory for all significant predictors except physical activity (3 categories) and number of risk factors. However, the assumption was found to be satisfactory for the time-updated analyses of these variables. All tests were 2-tailed and the level of significance was set at  $P < 0.05$ . Statistical analyses were performed with SAS statistical software (version 9.4; SAS Institute Inc., Cary, NC).

## Results

### Baseline Characteristics

The baseline cardiovascular risk factors in the 2 cohorts of 50-year-old men are presented in Table 1. Although 38% of cohort 1943 compared with 17.3% of cohort 1913 had 0 or only 1 risk factor, 30% of cohort 1943 still had at least 3 risk factors (Table 1).

### Risk of CVD and Death Over 2 Decades in Both Cohorts

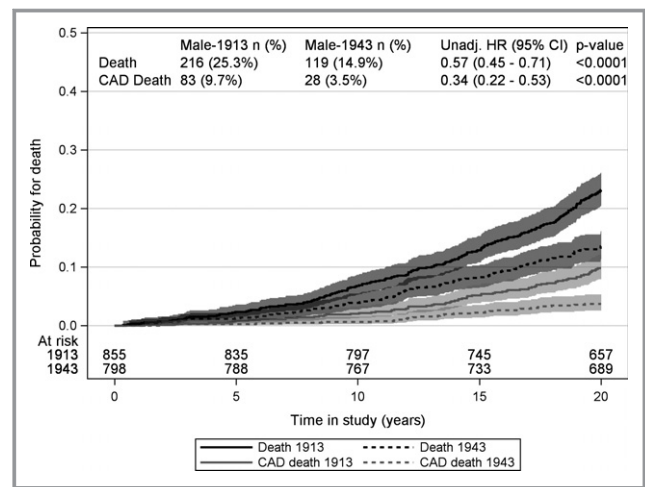
Both cohorts were followed for 21 years from age 50 years (ie, a total of 16 373 and 15 715 person-years). Both overall death rate and CAD death rates were significantly lower in cohort 1943 compared with cohort 1913. In cohort 1913, 25.3% (13.2 per 1000 observation years) died during follow-

**Table 1.** Baseline Data for Risk Factors for CVD in 50-Year-Old Men in Cohort 1913 and Cohort 1943

|  | Men Born in 1913 (n=855) | Men Born in 1943 (n=798) | P Value |
|--|--------------------------|--------------------------|---------|
| BMI (kg/m <sup>2</sup> )                     | 24.8 (3.2)               | 26.2 (3.4)               | <0.0001 |
| BMI ≥25 kg/m <sup>2</sup>                    | 371 (43.6%)              | 494 (61.9%)              | <0.0001 |
| BMI ≥30 kg/m <sup>2</sup>                    | 51 (6.0%)                | 101 (12.7%)              | <0.0001 |
| Systolic blood pressure (mm Hg)              | 138.3 (20.9)             | 128.7 (17.1)             | <0.0001 |
| Diastolic blood pressure (mm Hg)             | 91.6 (13.2)              | 84.4 (10.6)              | <0.0001 |
| Hypertension                                 | 580 (67.8%)              | 314 (39.3%)              | <0.0001 |
| Antihypertensive medication                  | 14 (1.6%)                | 50 (6.3%)                | <0.0001 |
| <b>Smoking</b>                               |                          |                          |         |
| Never-smoker                                 | 207 (24.2%)              | 258 (32.3%)              |         |
| Ex-smoker                                    | 168 (19.6%)              | 293 (36.7%)              |         |
| Smoker                                       | 480 (56.1%)              | 247 (31.0%)              | <0.0001 |
| Diabetes mellitus                            | 11 (1.3%)                | 32 (4.0%)                | 0.0008  |
| Total cholesterol (mmol/L)                   | 6.42 (1.12)              | 5.88 (1.04)              | <0.0001 |
| Cholesterol >6.2 mmol/L                      | 478 (55.9%)              | 284 (35.6%)              | <0.0001 |
| <b>Physical activity</b>                     |                          |                          |         |
| Sedentary leisure time                       | 295 (35.3%)              | 125 (15.7%)              |         |
| Moderate exercise during leisure time        | 270 (32.3%)              | 491 (61.5%)              |         |
| Regular exercise and training                | 271 (32.4%)              | 182 (22.8%)              | 0.0056  |
| <b>Number of cardiovascular risk factors</b> |                          |                          |         |
| 0  | 19 (2.3%)                | 91 (11.4%)               |         |
| 1  | 125 (15.0%)              | 212 (26.6%)              |         |
| 2  | 246 (29.5%)              | 259 (32.5%)              |         |
| 3  | 259 (31.1%)              | 166 (20.8%)              |         |
| 4  | 148 (17.7%)              | 53 (6.6%)                |         |
| 5  | 36 (4.3%)                | 17 (2.1%)                |         |
| 6  | 1 (0.1%)                 | 0 (0.0%)                 | <0.0001 |

Continuous variables are presented as mean (SD). Proportions are presented as n (%). Number of CVD risk factors was defined as sum of overweight, hypertension, being a smoker, diabetes mellitus, hyperlipidemia, and sedentary leisure time. BMI indicates body mass index; CVD, cardiovascular disease.

up; 9.7% (5.1 per 1000) from CAD (Figure 1, Table 2). In cohort 1943, there were 119 deaths (14.9%) and 28 CAD deaths (3.5% of the men in the cohort) during follow-up, corresponding to 7.6 and 1.8 per 1000 observation years, respectively. The probability of survival for 10 years was 0.96 (95% confidence interval [CI], 0.95–0.97) and for 21 years 0.85 (95% CI, 0.82–0.87). Thirty percent of all deaths in cohort 1943 were caused by CVD defined according to SCORE (Table 3).



**Figure 1.** Kaplan–Meier estimates of all-cause mortality and CAD death over a 21-year period in 50-year-old men from cohort 1913 and cohort 1943. CAD indicates coronary artery disease; CI, confidence interval; HR, hazard ratio.

Of the 798 participants in cohort 1943, 38 were excluded because of existing nonfatal CVD before the start of the study, leaving 760 participants for the analysis of CVD events (fatal or nonfatal) during follow-up. During a median follow-up of 20.5 (interquartile range 15.6–20.9) years, 233 participants (30.7%) experienced at least 1 CVD event, with an event rate (95% CI) per 1000 person-years at risk of 17.4 (15.2–19.8). Of the first 233 CVD events, 41% were attributable to CAD, 23% to cerebral vascular disorders, 22% to AF, and 11% to heart failure (Table 3).

### Risk Factors for CVD and All-Cause Death Over 2 Decades

In general, we observed only minor differences in the risk factors for CVD and all-cause death. Hypertension, smoking, diabetes mellitus, high serum cholesterol, and sedentary lifestyle at baseline were all associated with an increased incidence of CVD (Figure 2), whereas diabetes mellitus, smoking, and physical inactivity were strongly associated with the risk of death (Figure 3). However, the time-updated analyses including most current values over the subsequent 21 years showed greater effects for overweight (HR=1.44, 95% CI, 1.04–1.90; P=0.0099) and physical inactivity (sedentary leisure versus regular exercise HR=2.47, 95% CI, 1.64 to 3.70; P<0.0001, and moderate versus regular exercise HR=1.64, 95% CI, 1.17–2.31; P=0.0046), whereas the effect of high cholesterol values was reduced (Figures 4 and 5). Except for physical inactivity, no statistically significant interaction by birth cohort in contribution of risk factors to death was found between the 2 cohorts (Figure 3).

**Table 2.** Comparison of CAD Death and All-Cause Death in Cohort 1913 and Cohort 1943

| Cohort                 | n (%)<br>Events | Event Rate (95% CI)<br>Per 1000 Person Years | HR (95% CI)                          | Adjusted*<br>HR (95% CI)            |
|------------------------|-----------------|--|--------------------------------------|-------------------------------------|
| <b>CAD death</b>       |                 |  |                                      |                                     |
| Men born in 1913       | 83 (9.7%)       | 5.07 (4.09–6.29)                             | 1.00                                 | 1.00                                |
| Men born in 1943       | 28 (3.5%)       | 1.78 (1.23–2.58)                             | 0.34 (0.22–0.53)<br><i>P</i> <0.0001 | 0.57 (0.34–0.94)<br><i>P</i> =0.029 |
| <b>All-cause death</b> |                 |  |                                      |                                     |
| Men born in 1913       | 216 (25.3%)     | 13.19 (11.55–15.07)                          | 1.00                                 | 1.00                                |
| Men born in 1943       | 119 (14.9%)     | 7.57 (6.33–9.06)                             | 0.57 (0.45–0.71)<br><i>P</i> <0.0001 | 0.82 (0.62–1.07)<br><i>P</i> =0.14  |

BMI indicates body mass index; CAD, coronary artery disease; CI, confidence interval; HR, hazard ratio.

\*Adjusted for BMI, hypertension, systolic blood pressure, smoking, diabetes mellitus, serum cholesterol, and physical activity.

### Effects of Aggregate Risk Burden for CVD and All-Cause Death Over 2 Decades in Cohort 1943

When individuals were stratified by their burden of risk factors at 50 years of age, the long-term CVD risk rose markedly with increasing numbers of risk factors. CVD occurred in 17.8% of the participants with no risk factors, in 41.1% of those with 3 risk factors (HR=2.84, 95% CI, 1.64–4.92; *P*=0.0002), in 45.1% of those with 4 risk factors (HR=3.29, 95% CI, 1.74–6.24;

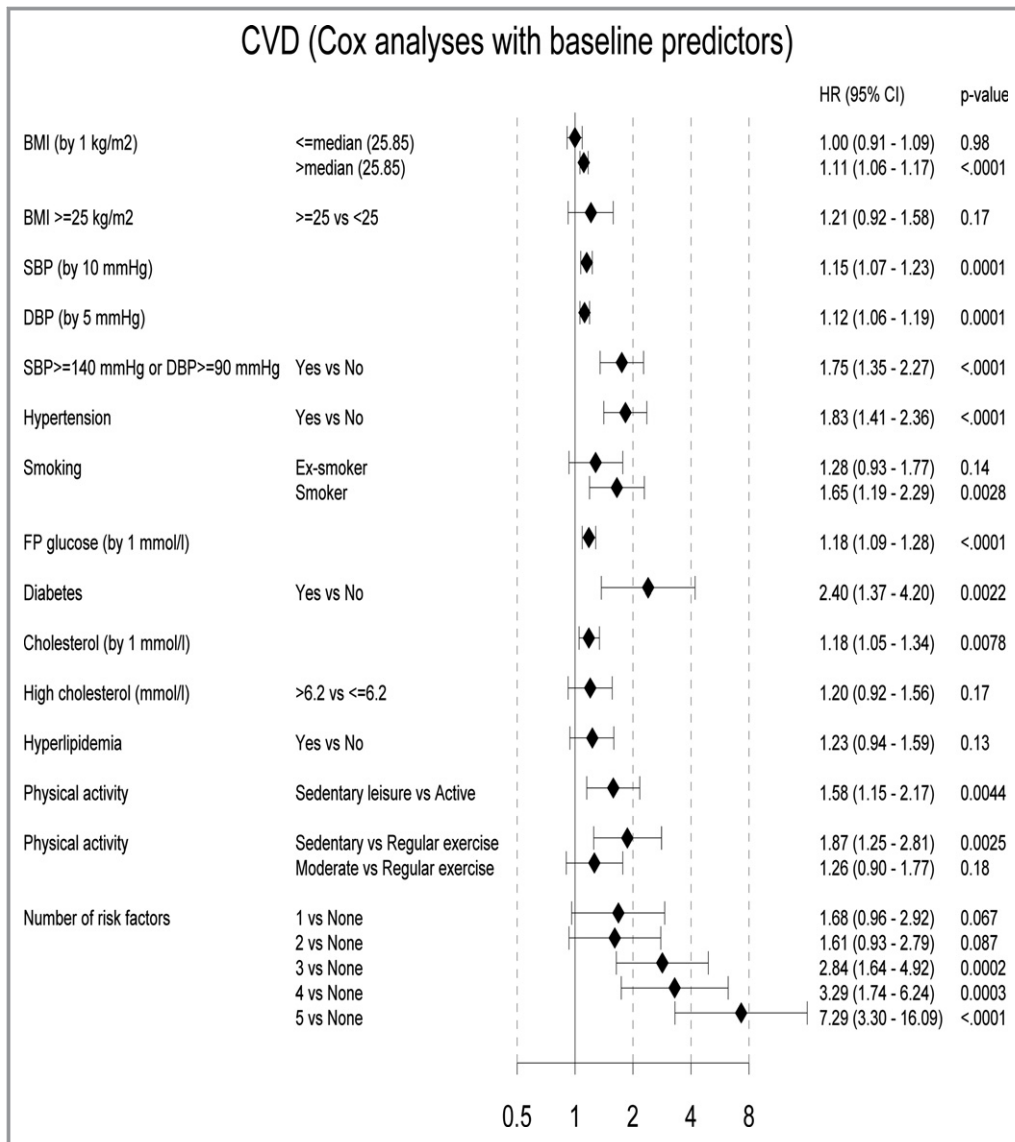
*P*=0.0003), and in 62.5% of those with 5 risk factors (HR=7.29, 95% CI, 3.30–16.09; *P*<0.0001) (Figure 6). Similarly, the long-term risk of all-cause death rose steeply with the number of risk factors (Figure 7). Death occurred in 7.7% of participants with no cardiovascular risk factors, in 11.9% of those with 1 to 2 risk factors, and in 19.3% (HR=2.65, 95% CI, 1.17–6.01; *P*=0.020), 28.3% (HR=4.09, 95% CI, 1.67–10.03; *P*=0.0021), and 52.9% (HR=8.98, 95% CI, 3.34–24.15; *P*<0.0001) of those with 3, 4, and 5, risk factors, respectively. No statistically significant

**Table 3.** Number of CVD Events, CVD Deaths (SCORE), and Event Rate Per 1000 Person-Years Over 21 Years of Follow-Up of Cohort 1943 (n=760).\*

|                                | Events n (%) | Follow-Up Y<br>Median (IQR) | Event Rate (95% CI)<br>Per 1000 Person-Years | Probability of Not<br>Experiencing End<br>Point At 10-Y Follow-Up<br>(95% CI) | Probability of Not<br>Experiencing<br>End-Point At 21-Y<br>Follow-Up (95% CI) |
|--------------------------------|--------------|-----------------------------|--|---|---|
| Cardiovascular disease         | 233 (30.7%)  | 20.5 (15.6–20.9)            | 17.38 (15.22–19.76)                          | 0.91 (0.88–0.92)  | 0.66 (0.63–0.70)  |
| CAD death                      | 17 (2.2%)    | 20.5 (15.6–20.9)            | 1.27 (0.74–2.03)                             | 1.00 (0.99–1.00)  | 0.97 (0.96–0.98)  |
| Myocardial infarction          | 48 (6.3%)    | 20.5 (15.6–20.9)            | 3.58 (2.64–4.75)                             | 0.96 (0.95–0.98)  | 0.93 (0.90–0.94)  |
| Heart failure                  | 25 (3.3%)    | 20.5 (15.6–20.9)            | 1.86 (1.21–2.75)                             | 1.00 (0.99–1.00)  | 0.94 (0.90–0.94)  |
| Atrial fibrillation            | 52 (6.8%)    | 20.5 (15.6–20.9)            | 3.88 (2.90–5.09)                             | 0.98 (0.97–0.99)  | 0.92 (0.89–0.93)  |
| TIA                            | 16 (2.1%)    | 20.5 (15.6–20.9)            | 1.19 (0.68–1.94)                             | 1.00 (0.99–1.00)  | 0.97 (0.96–0.98)  |
| Unstable angina                | 14 (1.8%)    | 20.5 (15.6–20.9)            | 1.04 (0.57–1.75)                             | 0.99 (0.98–1.00)  | 0.98 (0.96–0.99)  |
| Acute brain infarction         | 30 (3.9%)    | 20.5 (15.6–20.9)            | 2.24 (1.51–3.19)                             | 0.98 (0.97–0.99)  | 0.95 (0.93–0.97)  |
| Acute cerebral hemorrhage      | 7 (0.9%)     | 20.5 (15.6–20.9)            | 0.52 (0.21–1.08)                             | 1.00 (0.99–1.00)  | 0.99 (0.98–1.00)  |
| PCI                            | 8 (1.1%)     | 20.5 (15.6–20.9)            | 0.60 (0.26–1.18)                             | 1.00 (0.99–1.00)  | 0.99 (0.98–0.99)  |
| CABG                           | 9 (1.2%)     | 20.5 (15.6–20.9)            | 0.67 (0.31–1.27)                             | 0.99 (0.99–1.00)  | 0.98 (0.97–0.99)  |
| Open arterial vascular surgery | 4 (0.5%)     | 20.5 (15.6–20.9)            | 0.30 (0.08–0.76)                             | 1.00 (0.99–1.00)  | 0.99 (0.98–1.00)  |
| Transluminal vascular surgery  | 3 (0.4%)     | 20.5 (15.6–20.9)            | 0.22 (0.05–0.65)                             | 1.00 (1.00–1.00)  | 0.99 (0.98–1.00)  |
| CVD death (SCORE)              | 36 (4.7%)    | 20.6 (20.4–21.0)            | 2.40 (1.68–3.32)                             | 0.99 (0.98–1.00)  | 0.95 (0.93–0.96)  |

CABG indicates coronary artery bypass graft; CAD, coronary artery disease; CI, confidence interval; CAD death, death caused by CAD; CVD, cardiovascular disease; CVD death (SCORE), death caused by CVD based on definition of SCORE; IQR, interquartile range; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

\*Only the first CVD Event was recorded.



**Figure 2.** Cox analysis of CVD using baseline data from cohort 1943. Number of risk factors: BMI >25, hypertension, smoking, diabetes mellitus, and hyperlipidemia, sedentary leisure. BMI indicates body mass index; CI, confidence interval; CVD, cardiovascular diseases; DBP, diastolic blood pressure; FP glucose, fasting plasma glucose test; HR, hazard ratio; SBP, systolic blood pressure.

interaction by birth cohort in contribution of aggregate risk factors to death was found between the 2 cohorts (Figure 3).

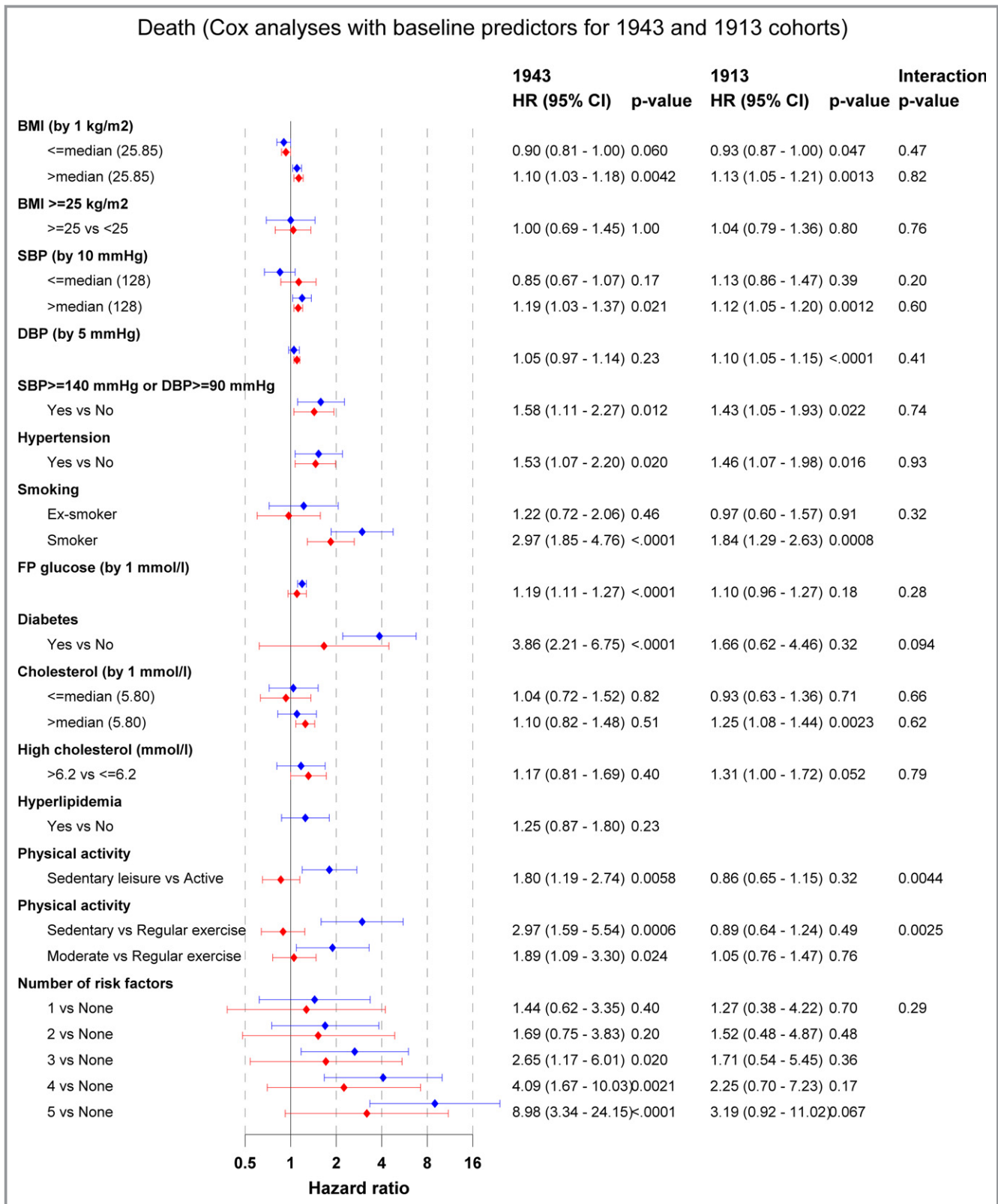
## Discussion

In this study, we demonstrated that despite a marked decrease in CAD mortality compared with cohort 1913, >30% of the men in the contemporary cohort 1943 developed CVD between the ages of 50 and 71 years, and 15% died. The aggregated burden of modifiable risk factors still had a striking effect, not only on the development of CVD, but also on overall mortality. Moreover, no statistically significant

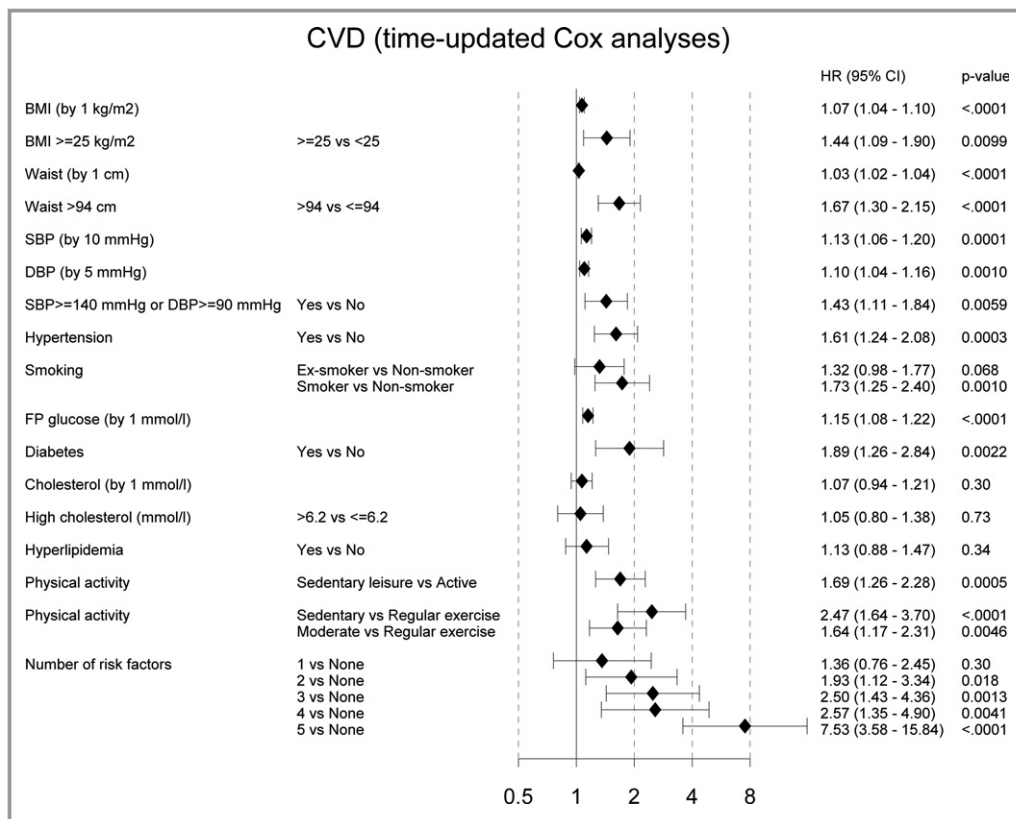
interaction by birth cohort in contribution of aggregate risk factors to death was found between 2 cohorts.

## Long-Term Risk of CVD and Death

The current European guidelines recommend that the global 10-year risk of fatal CVD or major CVD events should be estimated. However, it is inappropriate to make such an estimation based only on short-term risk factors, largely because the cardiovascular risk factor profile has changed dramatically in recent decades and its ultimate effect in the long term or over a lifetime may differ. A single risk factor can result in a cumulative high risk if left untreated, and lifestyle and risk factor patterns in



**Figure 3.** Cox analysis of all-cause death using baseline data from cohorts 1913 and 1943. Number of risk factors: BMI >25, hypertension, smoking, diabetes mellitus, hyperlipidemia, and sedentary leisure. Blue diamond: cohort 1943; red diamond: cohort 1913; BMI indicates body mass index; CI, confidence interval; DBP, diastolic blood pressure; FP glucose, fasting plasma glucose test; HR, hazard ratio; SBP, systolic blood pressure.



**Figure 4.** Time-updated analysis of CVD over a 21-year period in 50-year-old men from cohort 1943. BMI indicates body mass index; CI, confidence interval; CVD, cardiovascular diseases; DBP, diastolic blood pressure; FP glucose, fasting plasma glucose test; HR, hazard ratio; SBP, systolic blood pressure.

the general population may change over time. The lifetime risk for CVD in men from 50 to 95 years of age (a span of 45 years) reported in the Framingham Heart Study was 41% (95% CI, 38.8–43).<sup>15</sup> However, comparing these data with those obtained in the present study is problematic, because of differences in ethnicity, lifestyle, definitions of CVD, and study design. For instance, in the Framingham study, heart failure was not included in the definition of CVD. Nevertheless, the lifetime risk of CVD is higher than that of other diseases, including most common cancers, where, at 50 years of age, the lifetime risk of breast cancer in women is 13% and of prostate cancer in men is 19%.<sup>16</sup>

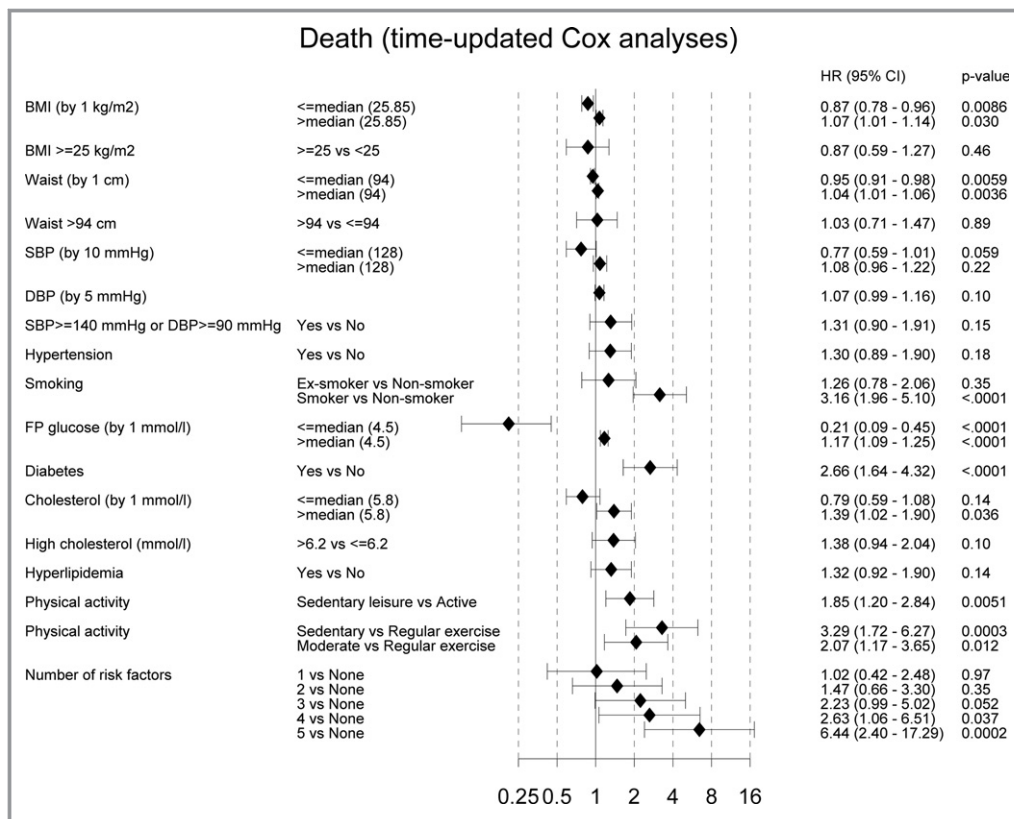
By comparing 2 study cohorts of the same age (50-year-old men) but born 30 years apart and who lived in the same area, and by applying the same methodology for ascertaining all-cause mortality and CAD death, we identified a reduction in all-cause mortality from 25% to 15%, and a reduction in CAD deaths by two thirds. Prior research has identified decreasing risk factors, mainly serum cholesterol and smoking, as main drivers of this reduction on a national level.<sup>4</sup> Similarly, the proportion of CAD deaths decreased markedly from 34% to 24% of all deaths, however, with CVD defined according to SCORE causing 30% of all deaths in the 1943 cohort.

Therefore, the majority of the deaths were from non-CVD causes. Despite this, an accumulation of CVD risk factors was associated with very high relative and absolute risks of death, conceivably because many CVD risk factors, including sedentary lifestyle, obesity, and smoking, are also linked with cancer risk.<sup>17</sup>

### Impact of Risk Factors

Recommendations to treat or modify risk factors can have unpredictable outcomes on the long-term effects of these risk factors on CVD or death. Our findings are valuable from a couple of critical points. First, despite improved knowledge about modification and treatment of risk factors, diabetes mellitus and hypertension are still associated with increased long-term risk of CVD. It is not clear whether this remaining high-risk profile implies that diabetes mellitus and hypertension per se represent an “irreversible” progressive cardiovascular continuum and/or whether current therapy is suboptimal. Second, in individuals aged 50 years, the effect of sedentary leisure on the development of CVD was initially similar to that of hypertension and smoking, but became more apparent during the follow-up, with sedentary leisure having





**Figure 5.** Time-updated analysis of death over a 21-year period in 50-year-old men from cohort 1943. BMI indicates body mass index; CI, confidence interval; DBP, diastolic blood pressure; FP glucose, fasting plasma glucose test; HR, hazard ratio; SBP, systolic blood pressure.

the highest HR of any single risk factor. Because physical inactivity is known to be related to decreased insulin sensitivity, elevated blood pressure, and overweight, this might explain why sedentary leisure was not an independent risk factor for the development of CVD in multivariable analysis; ie, the effect of sedentary leisure may be masked by competition with other risk factors. Our findings demonstrate almost identical risk factor profiles for all-cause death and CVD, illustrating that CVD and death share common risk factors.

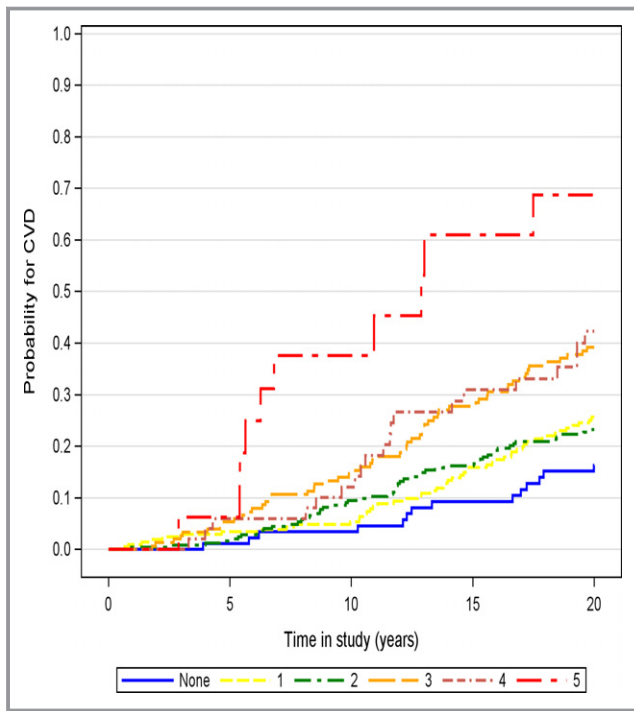
The study demonstrates a huge difference in long-term risk of both CVD and death between those with no risk factors and those with  $\geq 3$  risk factors at baseline. These differences persisted throughout the 21-year follow-up. The only clear change in risk factors was observed in physical activity and the only statistically significant interaction with death out of studied risk factors in the 2 cohorts was seen here. This might be explained by the fact that participants in the cohort 1913 had to be more physically active in their work and commuting, as compared to the 1943 cohort. Taken together, our results confirm that what matters most for an individual is their total risk.

Our study adds to the current literature because our results are based not only on measurements at an index age

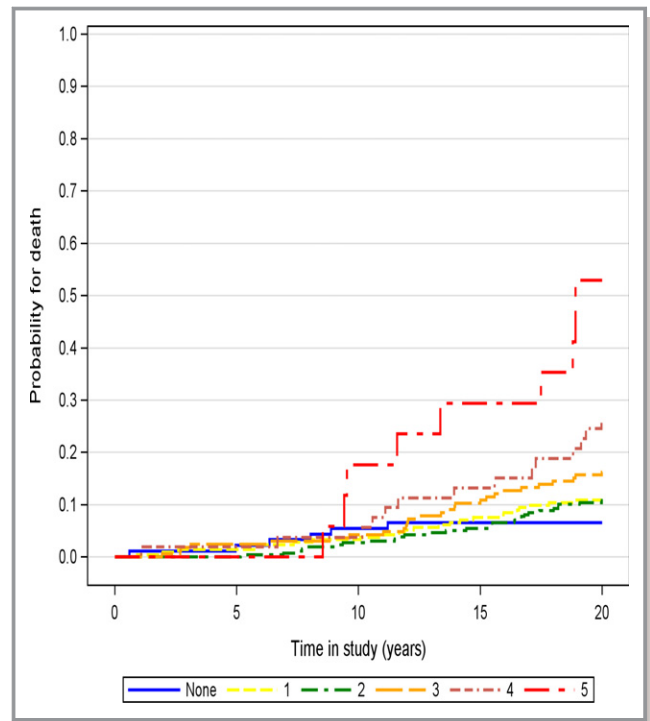
but also on repeated measurements during 2 decades of follow-up. This is important considering the widespread guidelines recommending cardiovascular preventive measures and the crossover that is likely to occur over a long period.

### Limitations and Strengths

The fairly small sample size is a limitation, as is the comparatively low participation rate in the cohort 1943. Given that nonparticipants may be assumed to be less healthy,<sup>18</sup> total CVD events and mortality in cohort 1943 will probably be underestimated. Another limitation is that we cannot compare the occurrence of CVD events between the 2 cohorts because they were studied 30 years apart and some examinations (eg, echocardiography and thumb ECG) were not performed for cohort 1913. Therefore, we were unable to compare the composite of all CVD events between the 2 cohorts because we lacked information in the cohort 1913 about important components such as heart failure, unstable angina, and AF where diagnostic practices have changed considerably. The all-male study population is another limitation. The fact that the participant rates were 88% among men born in 1913 and 55% in men born in 1943 might have affected the results. Declining participation rates in



**Figure 6.** Kaplan–Meier estimates of aggregate risk burden for CVD from cohort 1943 according to number of risk factors: (BMI >25, hypertension, smoking, diabetes mellitus, hyperlipidemia, or sedentary lifestyle). BMI indicates body mass index; CVD, cardiovascular diseases.



**Figure 7.** Kaplan–Meier estimates of aggregate risk burden for all-cause death from cohort 1943. According to number of risk factors: (BMI >25, hypertension, smoking, diabetes mellitus, hyperlipidemia, or sedentary lifestyle). BMI indicates body mass index.

epidemiological studies is a major problem when comparing trends, and a mean decline in participation rate of 0.67% per year in cross-sectional studies between 1970 and 2003 has been reported.<sup>19</sup> The ethnicity of the 2 cohorts also differs slightly. In the cohort of men born in 1913, only 5% were born outside of Sweden, while in the cohort of men born in 1943, 17% were born in another country. The strengths of the study are that we analyzed random population samples, all of the same sex and age and free of prior CVD. We also compared 2 cohorts living in the same geographic area using exactly the same methodology. The availability of nationwide registers allowed us to identify all hospitalizations for major CVD, and all deaths occurring over the extended follow-up in the cohort 1943.

### Clinical Implications

Our findings are clinically relevant because, first, both all-cause mortality and CAD death have substantially reduced over the past 30 years. Even so, morbidity in men born in the 1940s is still quite substantial, which should be taken into account when allocating resources for health care. Second, the current European CVD risk assessment model (SCORE risk charts) needs to be continuously updated, and has, in

fact, already been updated for Sweden, where a recent study showed that the group with a high risk of fatal CVD as defined by SCORE no longer carries this high risk because of improved cardiovascular preventative care.<sup>14</sup> Third, our finding of an association between CVD risk factors and all-cause death illustrate that CVD- and non-CVD-related death share many of the same risk factors. Therefore, it is time to focus more on global than on disease-specific risk factors.

### Conclusion

By comparing 2 randomly selected, population-based cohorts from the same area, 30 years apart, studied with similar methods and with a long-term follow-up, we demonstrated that despite a marked reduction in CAD death over the past 30 years and a new era of CVD prevention, early and intensive modification of risk factors in 50-year-old men from the general population is still crucial. These factors contribute to both the continuing high risk of CVD events and to premature death.

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## Disclosures

None.

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