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Risk Factor Burden in Middle Age and Lifetime Risks for Cardiovascular and Non-Cardiovascular Death (Chicago Heart Association Detection Project In Industry)

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Abstract

Data are sparse regarding the association of risk factor burden in middle age with lifetime risks for cardiovascular disease (CVD) and non-CVD death. We stratified participants of the Chicago Heart Association Detection Project in Industry aged 40 to 59 years in 1967–1973 into 5 groups based on risk factor burden: favorable risk factor profile (untreated blood pressure $\leq 120/\leq 80$ mm Hg, total cholesterol < 200 mg/dL, non-smoking, and body mass index [BMI] < 25 kg/m²); 0 elevated but ≥ 1 unfavorable; or any 1, any 2, or ≥ 3 elevated (systolic ≥ 140 or diastolic ≥ 90 mm Hg, or treated hypertension; total cholesterol ≥ 240 mg/dL; current smoking; or BMI ≥ 30 kg/m²). We estimated remaining lifetime risks for CVD and non-CVD death through age 85 years. We followed 8033 men and 6493 women for 409,987 person-years; 2582 died of CVD and 3955 died of non-CVD causes. Greater risk factor burden was associated with higher incidence of both CVD and non-CVD death. Compared with participants with ≥ 3 risk factors, those with favorable profiles had substantially lower lifetime risks for CVD death (20.5% vs. 35.2% in men, 6.7% vs. 31.9% in women) and markedly longer median Kaplan-Meier survival (> 35 vs. 26 years in men, > 35 vs. 28 years in women). In conclusion, having favorable risk factors in middle age is associated with lower lifetime risk for CVD death and markedly longer survival. These results should encourage efforts aimed at preventing development of risk factors in younger individuals to decrease CVD mortality and promote longevity.

Keywords

cardiovascular disease; prognosis; epidemiology; risk factors

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The associations of traditional risk factors with cardiovascular disease (CVD), established in short-term studies, may be unpredictable over long-term follow-up. For example, the relative risks associated with some risk factors tend to diminish with advancing age,¹ and smoking increases risk for CVD but also markedly increases the competing risk for death from cancer and lung diseases.^{2,3} The association of CVD risk factors with *non*-CVD death^{4,5} is not widely appreciated, but it could create an important competing risk as well. Because of the potential for changes in risk factor associations with aging and for competing risks, the population burden of CVD cannot be predicted reliably from short-term studies using traditional epidemiologic methods. To date, only one study has examined lifetime risks for CVD endpoints according to aggregate risk factor burden at a single age.² Therefore, we sought to estimate lifetime risks for CVD and non-CVD death and median survival by risk factor strata in middle-aged men and women from the Chicago Heart Association Detection Project in Industry (CHA study).

METHODS

Study sample

Entry criteria and methods of the Chicago Heart Association Detection Project in Industry have been published previously.⁶ Briefly, from November 1967 to January 1973, the CHA study screened 39,523 men and women aged 18 years and older of varied socioeconomic backgrounds and ethnicities employed at 84 Chicago-area businesses and organizations. As previously reported in detail, standardized examination methods were used.^{7,8} Trained staff measured supine blood pressure using a standard mercury sphygmomanometer, and serum total cholesterol from a non-fasting blood sample.⁹ Participants completed a questionnaire about their demographic characteristics, smoking history (never, former, or current smoking, and number of cigarettes/day for current smokers), medical diagnoses and treatments (including hypertension and diabetes). Resting electrocardiograms were classified as showing major, minor, or no abnormalities, according to the standardized definitions used in the Hypertension Detection and Follow-up Program.¹⁰ The study has been approved periodically by the Northwestern University Institutional Review Board.

For the present study, we sought to examine remaining lifetime risks among middle-aged individuals free of CVD at baseline. From the 39,523 participants in the cohort, we excluded those with: baseline age <40 or ≥60 (n=22,273); history of myocardial infarction (n=313); ≥1 major electrocardiographic abnormalities (n=1,563); prevalent self-reported diabetes (since the duration of diabetes was not ascertained; n=498); or missing risk factor or follow-up information (n=350). The sample for this study therefore included 14,526 men and women aged 40 to 59 years at baseline.

Risk factor groups

Clinical cut-off values from national guidelines^{11–13} were used to define favorable, unfavorable and elevated levels of blood pressure, serum cholesterol, and body mass index. In addition, current smoking was considered to be an elevated risk factor, as was use of antihypertensive medications for blood pressure. Participants were stratified into 5 mutually exclusive groups, as follows, based on their aggregate risk factor burden at the baseline examination: favorable risk factor profile, 0 elevated risk factors (but ≥1 unfavorable), any 1, any 2, or ≥3 elevated risk factors (see Table 1 for definitions).

Mortality follow-up

Vital status was ascertained through 2002, with average follow-up of 32 years. Prior to 1979, follow-up was completed by direct mail, telephone, contact with employer, and matching of records with Social Security Administration files; from 1979 to 1994 the National Death Index (NDI) was used to identify deaths.¹⁴ Death certificates were obtained and coded for underlying

causes by trained researchers according to the Eighth Revision of the International Classification of Diseases (ICD-8).¹⁵ Subsequently, the NDI-*plus* service was used to obtain ICD Ninth Revision (ICD-9) underlying cause of death coding for 1995–98 and ICD Tenth Revision (ICD-10) coding from 1999–2002.^{16,17} Deaths from CVD were defined as underlying cause of death as listed on the death certificate using the ICD-8 codes 390–459 for deaths occurring prior to 1995, ICD-9 codes 390–459 (1995–1998), and ICD-10 codes I00–I99 (1999–2002). All other underlying causes of death, including those that were indeterminate, were assigned as non-CVD deaths.

Statistical analysis

All statistical analyses were performed using SAS statistical software, version 9.1 (SAS Institute, Inc.; Cary, NC). We first generated the Kaplan-Meier cumulative incidences¹⁸ for CVD death and for non-CVD death, according to strata of aggregate risk factor burden. For calculation of lifetime risk, a modified technique of survival analysis was used, as described previously.^{19,20} In this type of analysis, participants contribute information on the incidences of CVD and death free of CVD for each age they attain during follow up. Participants enter the sample at any age older than 39 years and contribute person-time to follow up. Age-specific hazards, incidence rates, cumulative incidence, and survival probabilities were calculated as in a Kaplan-Meier analysis.¹⁸ Since the Kaplan-Meier cumulative incidence does not reflect the competing risk for death from other causes, adjustment to age-specific incidences of CVD death was made for the competing risk, and adjusted age-specific incidences were summed to yield a true remaining lifetime risk for CVD death.¹⁹ Each subject in the study sample was followed from entry until the occurrence of CVD death, non-CVD death, or the end of follow up in 2002. Lifetime risk estimates for CVD and Kaplan-Meier overall survival were calculated for men and women separately in each risk factor stratum. Lifetime risk estimates and cumulative incidences are presented through age 85 years only, because of limited number of person-years of follow up beyond age 85.

RESULTS

Study sample

The study sample included 8033 men and 6493 women aged 40 to 59 years, including 414 black men and 368 black women. During 409,987 person-years of follow-up, there were 2582 deaths due to CVD and 3955 non-CVD deaths. Table 1 shows the number of men and women and the number of CVD deaths during follow up in each stratum of risk factor burden. Overall 17.5% of men and 23.3% of women had favorable risk factor profiles or no elevated risk factors, whereas more than 75% of men and women had at least one elevated risk factor.

Unadjusted risks for CVD and non-CVD death

Kaplan-Meier unadjusted cumulative incidence curves for CVD death over an average of 32 years of follow-up are shown in Figure 1A, separately for men and women. With higher risk factor burden, cumulative incidence of CVD death was substantially higher. Of note, higher risk factor burden was *also* associated with substantially greater risk for non-CVD death in both men and women (Figure 1B). The data in Table 2 also show that hazards ratios for non-CVD death increase substantially with greater CVD risk factor burden. The strong association of risk factor burden with non-CVD death suggests that the competing risk of non-CVD death could reduce the lifetime risk for CVD associated with higher burden of traditional risk factors.

Lifetime risks for CVD death in middle age

The cumulative risk curves for CVD death (adjusted for the competing risk of non-CVD death) are shown in Figure 2. Remaining lifetime risks for CVD death according to aggregate risk

factor burden in middle age are shown in Table 3. Individuals with favorable risk factor profiles in middle age had low lifetime risks for CVD death. Because there were few men in the favorable profile group, the confidence intervals are wide for this estimate. With greater risk factor burden in middle age, the lifetime risks for CVD death through age 85 increased substantially for men and women. Concurrently, overall median survival decreased substantially with higher risk factor burden (Table 3). Men with ≥ 3 elevated risk factors in middle age had an average lifetime risk for CVD death nearly 2 times higher and a median survival more than 9 years shorter than men with a favorable profile. Similarly, women with ≥ 3 risk factors had an average lifetime risk for CVD death approximately 5 times higher and a median survival more than 7 years shorter than women with a favorable profile. Lifetime risks for death due to coronary heart disease alone (data not shown) revealed a similar pattern of association with risk factor burden as lifetime risks for CVD death.

Comparison of the unadjusted Kaplan-Meier cumulative incidence for CVD death with the lifetime risk for CVD death illustrates the importance of accounting for competing risks (Table 4). There were relatively small differences between unadjusted cumulative incidences and lifetime risk estimates among individuals with favorable profiles or 0 elevated risk factors. With greater risk factor burden, the difference between the unadjusted Kaplan-Meier cumulative incidence and the lifetime risk estimate increased, indicating greater competing risk from non-CVD death.

DISCUSSION

In this large cohort, we observed that men and women with favorable risk factor profiles in middle age have a low remaining lifetime risk for CVD death, and prolonged survival. In contrast, greater risk factor burden in middle age is associated with higher risk for both CVD and non-CVD death. Despite the higher competing risk for non-CVD death in those with greater CVD risk factor burden in middle age, remaining lifetime risk for CVD death is substantially higher and median overall survival is dramatically lower compared to individuals with favorable profiles.

Our findings suggest that public health and clinical prevention efforts need to focus on individuals well before middle age, since even the presence of a single elevated risk factor in middle age is associated with substantially increased lifetime risk for CVD death and shorter survival. Of note, all of the risk factors that we examined are potentially preventable through appropriate diet and lifestyle choices at younger ages. Among individuals who already have ≥ 1 elevated risk factors in middle age, our data suggest that intensive global risk factor modification should be considered, given the associated high lifetime risks for CVD death and decreased longevity.

The large differences in lifetime risk for CVD death and median survival between participants with favorable risk factor profiles and those with ≥ 3 elevated risk factors were striking. Increasing interest is being focused on individuals with optimal or low levels of traditional risk factors. In addition to substantially lower risks for cardiovascular disease, cardiovascular death, and total mortality,^{4,21,22} individuals with low risk factor levels in middle age also appear to have fewer comorbidities at older ages. Data from the CHA cohort indicate that individuals with favorable risk profiles in middle age who survive to older age have better health-related quality of life 25 years later, compared with those who have elevated risk factors in middle age.²³ These data underscore the importance of preventing the development of traditional risk factors at younger ages in order to increase healthy longevity in older adults.

The observation that CVD risk factors are associated with markedly increased risk for *non-CVD* death may not be novel, but this association is not widely appreciated. Examination of

Figure 1 indicates that the incidence of non-CVD death exceeds that for CVD death at all levels of CVD risk factor burden. Indeed, even among those with the greatest CVD risk factor burden, the risk for non-CVD mortality exceeds the risk for CVD mortality (although the curves in Figure are not adjusted for age). That lifetime risk for CVD death still increases so dramatically with higher risk factor burden, despite the increased competing risk from non-CVD death, indicates the importance of these risk factors. Nonetheless, our findings suggest the possibility that it may be difficult to improve CVD risk estimation using current multivariable equations^{11,24} by a substantial amount, given the effect of competing risks from non-CVD death associated with the same risk factors that are used to estimate multivariable CVD risk. Current risk equations^{11,24} do not account for these competing risks.

The present findings confirm and extend the results of a similar analysis from the Framingham Heart Study.² In that study, Framingham participants were stratified according to risk factor burden at age 50 and lifetime risks for atherosclerotic CVD were estimated. Compared with participants with ≥ 2 major risk factors, those with low risk factor levels had substantially lower lifetime risks (5.2% vs. 68.9% in men, 8.2% vs. 50.2% in women) and markedly longer median survivals (>39 vs. 28 years in men, >39 vs. 31 years in women).² The differences in lifetime risks between that study and the present one for those with high risk factor burden can be attributed to the inclusion of non-fatal as well as fatal events in the Framingham analysis.

To date, only a limited number of studies performed in exclusively white cohorts have examined lifetime risks for CVD events.^{25–29} To our knowledge, no published data are available regarding lifetime risks for CVD among other race/ethnic groups. The number of blacks in our study sample was limited, precluding our ability to compare outcomes directly by race. We had limited power to generate robust lifetime risk estimates for individuals with favorable risk factor profiles in middle age, resulting in wide confidence intervals. Pooling of multiple cohorts would be useful to include enough men and women with low risk factor burden to allow more precise estimates. Our findings may have been subject to some misclassification, since death certificates tend to over-diagnose coronary and/or cardiovascular disease as underlying causes of death.³⁰ Because of the nature of follow up in the CHA cohorts, we did not ascertain non-fatal CVD events. Had we been able to do so, the lifetime risks for all CVD (not just fatal CVD) among those with elevated risk factors would likely have been substantially higher. A limitation of Kaplan-Meier and lifetime risk estimation methods is that they allow only for single assignment into risk factor strata at baseline. Thus, our estimates for each stratum represent averages. Some individuals with low risk factor burden undoubtedly developed new risk factors as they aged, and some with high risk factors undoubtedly received treatment or modified their risk factors through lifestyle changes. Nonetheless, the estimates provided by our results represent useful clinical information, since the risk factor data are what would be available to a clinician and a patient at a given point in time (middle age), when future changes in risk factors or treatment would be difficult to predict. Likewise, our methods do not allow for adjustment for age or other covariates. Lifetime risk estimates may be somewhat subject to birth cohort effects, but inclusion of broad age ranges at baseline and use of long-term follow up tend to reduce birth cohort effects, since multiple individuals from different birth cohorts contribute to any given age-specific incidence of disease or non-disease mortality.

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Figure 1.

Kaplan-Meier cumulative incidence of death due to cardiovascular disease (CVD; Panel A) and non-cardiovascular causes (Non-CVD; Panel B), by risk factor (RF) burden in middle aged men and women, according to years of follow-up after baseline examination. See Table 1 for definitions.

Figure 2.

Cumulative risks for death due to cardiovascular disease (CVD), adjusted for the competing risk of non-cardiovascular disease death, by risk factor (RF) burden in men and women who were aged 40 to 59 years at baseline. The point at which a line intercepts the vertical axis at age 85 years represents the estimated remaining lifetime risk through age 85 years. See Table 1 for definitions.

Number of men and women in the study sample with specified risk factor levels, as defined, and who experienced cardiovascular disease (CVD) death during follow up.

Table 1

Aggregate Risk Factor Burden*	No. of Men (No. with CVD Death)	No. of Women (No. with CVD Death)
Favorable Risk Factor Profile	162 (22)	307 (12)
0 Risk Factors Elevated	1242 (143)	1209 (92)
Any 1 Risk Factor Elevated	3024 (553)	2564 (298)
Any 2 Risk Factors Elevated	2601 (644)	1828 (360)
3 or More Risk Factors Elevated	1004 (290)	585 (168)
Total	8033 (1652)	6493 (930)

Abbreviations: BMI denotes body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure.

* "Favorable risk factor profile" is defined as untreated SBP ≤120 mm Hg and DBP ≤80 mm Hg, and total cholesterol <200 mg/dL, and non-smoker, and BMI <25 kg/m²; "0 risk factors elevated" indicates no elevated risk factors, but 1 or more risk factors not at favorable levels; "elevated risk factors" include SBP ≥140 mm Hg or DBP ≥90 mm Hg or receiving antihypertensive therapy, total cholesterol ≥240 mg/dL, current cigarette smoking, or BMI ≥30 kg/m².

Age-adjusted hazards ratios for cardiovascular disease (CVD) and non-CVD death by aggregate risk factor burden in middle age.

Aggregate Risk Factor Burden*	Age-Adjusted Hazards Ratio for CVD Death (95% CI)		Age-Adjusted Hazards Ratio for Non-CVD Death (95% CI)	
	Men	Women	Men	Women
Favorable Risk Factor Profile	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
0 Risk Factors Elevated	0.9 (0.6–1.4)	1.6 (0.9–3.0)	1.3 (0.9–1.9)	1.0 (0.7–1.3)
Any 1 Risk Factor Elevated	1.5 (1.0–2.3)	2.5 (1.4–4.5)	1.9 (1.3–2.7)	1.4 (1.0–1.8)
Any 2 Risk Factors Elevated	2.3 (1.5–3.6)	4.4 (2.5–7.9)	2.6 (1.8–3.8)	1.9 (1.4–2.5)
3 or More Risk Factors Elevated	3.1 (2.0–4.8)	6.8 (3.8–12.3)	3.0 (2.1–4.5)	2.1 (1.6–3.0)

Abbreviation: CI indicates confidence interval.

* Definitions as in Table 1.

Table 2

Table 3
Lifetime risk for cardiovascular disease (CVD) death through age 85 years and median overall survival by aggregate risk factor burden in middle age.

Aggregate Risk Factor Burden*	Men		Women	
	Lifetime Risk for CVD Death (95% CI)	Median Survival (Years)	Lifetime Risk for CVD Death (95% CI)	Median Survival (Years)
Favorable Risk Factor Profile	20.5% (11.6–29.4%)	>35	6.7% (2.2–11.1%)	>35
0 Risk Factors Elevated	15.3% (12.5–18.0%)	>35	10.4% (7.9–13.0%)	>35
Any 1 Risk Factor Elevated	23.9% (21.9–25.9%)	33	13.9% (12.2–15.7%)	>35
Any 2 Risk Factors Elevated	29.4% (27.3–31.6%)	28	21.8% (19.6–24.0%)	32
3 or More Risk Factors Elevated	35.2% (31.5–38.8%)	26	31.9% (27.6–36.2%)	28

Abbreviations: CI indicates confidence interval.

* Definitions as in Table 1.

Table 4

Unadjusted Kaplan-Meier cumulative incidences compared with lifetime risk estimates for cardiovascular disease (CVD) death through age 85 years, by aggregate risk factor burden in middle age.

Aggregate Risk Factor Burden*	Men		Women	
	Unadjusted Cumulative Incidence	Lifetime Risk	Unadjusted Cumulative Incidence	Lifetime Risk
Favorable Risk Factor Profile	23.4%	20.5%	7.7%	6.7%
0 Risk Factors	18.0%	15.3%	12.0%	10.4%
Any 1 Risk Factor Elevated	30.3%	23.9%	16.8%	13.9%
Any 2 Risk Factors Elevated	39.3%	29.4%	27.3%	21.8%
3 or More Risk Factors Elevated	48.9%	35.2%	39.2%	31.9%

* Definitions as in Table 1.