

Traditional risk factors across short-, intermediate-, and long-term follow-up in men and women

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We found sex differences in the pattern of relative strength when risk-factor associations with death from cardiovascular disease (CVD) were evaluated across different periods of follow-up. In women, an increased risk in CVD-related death was associated with diabetes mellitus and smoking; this risk was most prominent in the early follow-up period. Our finding illustrates that clinicians should employ more intense preventive measures in women who are smokers or have diabetes.

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It is well established that traditional cardiovascular disease (CVD) risk factors, such as total serum cholesterol and systolic blood pressure measured at baseline, are associated with CVD over long periods (ie, 30 years) of follow-up. In addition, multiple studies have compared the strength of the association between these traditional risk factors and CVD across different periods of short-, intermediate-, and long-term follow-up in men. Although some studies have found that the relative risk associated with smoking and diabetes in women is 2 to 3 times greater than that of men in the short term (≤ 10 years), little is known about the association of these risk factors with CVD outcomes in women across longer periods of follow-up (eg, 10-20 years or >20 years).¹ We sought to shed light on this by comparing the strength of the association between traditional risk factors and CVD death in women and men across 3 distinct follow-up periods.

Methods

CHA (Chicago Heart Association Detection Project in Industry) is a well-established observational cohort study designed to assess the associations of traditional risk factors with CVD.^{2,3} Traditional risk factors and electrocardiograms (ECGs) were measured in accordance with standard protocols. Vital status was ascertained through 2003, with an average follow-up of 33 years. Mortality from coronary heart disease (eg, ischemic heart disease), CVD (eg, all circulatory diseases), and all other causes of death were assigned as non-CVD deaths in accordance with standard death certificate coding (ie, ICD-9 codes).

We included a total of 16,608 participants after excluding those with a history of myocardial infarction or with missing baseline covariates. The follow-up period was partitioned into 3 separate time periods: 0 to 10 years, 10 to 20 years, and more than 20 years. For example, an individual surviving for 25 years would provide 10 years of follow-up for the first interval (0-10 years), 10 years for the second interval (10-20 years), and 5 years for the third interval (>20 years). Cox proportional hazards models were constructed for each follow-up period. All models were multivariable and adjusted for all baseline covariates, including age, systolic blood pressure, total serum cholesterol, body mass index (BMI), smoking, diabetes mellitus, major ECG abnormalities, and minor ECG abnormalities. We examined for trends in the associations by testing the changes in the beta

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coefficients from the 3 time intervals using a chi-square test with 2 degrees of freedom. We interpreted a *P* value below .05 to suggest that the strength of the association between the risk factor and death from CVD was different across the follow-up periods.

Results

The baseline characteristics listed in **Table 1** reveal minor but expected sex differences with regard to systolic blood pressure, smoking, diabetes mellitus, and ECG abnormalities. As shown in **Table 2** and the **Figure**, systolic blood pressure, total serum cholesterol, current smoking, and diabetes mellitus were associated with CVD death during nearly all follow-up intervals in men and women. The hazard ratios for CVD death associated with systolic blood pressure differed across the follow-up periods, decreasing in later follow-up periods in both men and women. In contrast, the hazard ratios for total serum cholesterol were similar across all follow-up periods.

We noted important sex differences for other risk factors in association with CVD death. In men, the hazard ratio for diabetes mellitus remained unchanged across the follow-up periods. In contrast, the hazard ratio for diabetes mellitus in women showed a marked decrease in strength across the 3 distinct follow-up periods. Similar sex differences were observed for smoking. When examining BMI in men, the hazard ratio increased across the follow-up periods, whereas no change was observed in women. Last, the association of baseline major and minor ECG abnormalities with CVD death in men was very strong in the initial follow-up period, with significant attenuation in the subsequent

follow-up periods. In women, no consistent association was observed (**Table 2** and **Figure**).

Discussion

To our knowledge, this is the first report examining the association between baseline measures of traditional risk factors and CVD mortality in women across different intervals of follow-up. We found higher hazard ratios for diabetes mellitus and smoking in the first decade of follow-up in women compared with men, with substantial attenuation in risk over the second and third decades. In men, the hazard ratio for BMI was lower in the first decade of follow-up, with a progressive increase in risk observed over the subsequent follow-up periods. In addition, the hazard ratios for CVD death associated with major and minor electrocardiographic abnormalities in men were highest in the initial follow-up period, with significant attenuation

observed over the subsequent decades of follow-up.

The most significant difference between the sexes in risk for CVD from both diabetes mellitus and smoking occurred in the first 10 years. These findings provide further support for earlier, more intensive prevention strategies aimed at risk-factor modification in women with diabetes and in those who continue to smoke.⁴ Although the exact mechanism for these observed sex differences remains unclear, these findings are consistent with greater atherogenic effects of both smoking and diabetes in women.⁵

Several studies have previously reported the association between traditional risk factors and coronary heart disease across different periods of follow-up in men. In general, these studies have noted that the associated relative risk for smoking is highest during short-term follow-up (0-10 years) and weaker during later periods

Table 1. Baseline characteristics of 16,608 men and women 40 to 59 years of age between 1967 and 1973 from the CHA study.^a

Variable	Mean (SD)	
	Men (n = 9033)	Women (n = 7575)
Age, years	48.7 (5.6)	49.5 (5.4)
Systolic blood pressure, mm Hg	141.4 (19.8)	136.5 (20.2)
Total serum cholesterol, mg/dL	212.2	218.6
Body mass index, kg/m ²	27.2 (37.0)	25.2 (40.4)
Smoke, %		
Never	23.8	48.1
Former	34.7	15.7
Current	41.5	36.3
Cigarettes daily ^b	24 (12)	18 (10)
Diabetes mellitus, %	3.5	2.4
Major ECG abnormalities, %	7.6	11.8
Minor ECG abnormalities, %	7.2	4.7

CHA indicates Chicago Heart Association Detection Project in Industry; ECG = electrocardiogram; SD = standard deviation.

^aAll risk-factor differences by sex were statistically significant (*P* < .05).

^bAmong current smokers.

In the Heart of Women

Table 2. Multivariable-adjusted hazard ratios (95% CI) for CVD death for 0-10, 10-20, and more than 20 years of follow-up in 16,608 men and women between 40 and 59 years from the CHA study.

	0-10 Years		10-20 Years		>20 Years		P ^a
	HR	95% CI	HR	95% CI	HR	95% CI	
Men							
Systolic blood pressure (per 20 mm Hg)	1.37	1.24-1.50	1.33	1.24-1.44	1.18	1.11-1.25	.002
Total serum cholesterol (per 40 mg/dL)	1.19	1.10-1.29	1.19	1.10-1.29	1.11	1.04-1.18	.110
Smoke							
Never	1.0	-	1.0	-	1.0	-	
Former	0.93	0.65-1.31	1.09	0.86-1.38	1.23	1.06-1.44	.787
Current	1.86	1.37-2.53	2.10	1.69-2.62	1.67	1.44-1.95	
Body mass index (per 4 kg/m ²)	1.01	0.90-1.14	1.13	1.04-1.23	1.20	1.13-1.28	< .001
Diabetes mellitus	1.88	1.23-2.88	2.42	1.79-3.27	2.03	1.56-2.64	.368
Minor ECG abnormalities	2.14	1.52-3.03	1.07	0.80-1.43	1.28	1.04-1.56	< .001
Major ECG abnormalities	3.89	2.97-5.08	1.54	1.20-1.98	1.26	1.02-1.56	< .001
Women							
Systolic blood pressure (per 20 mm Hg)	1.57	1.30-1.91	1.37	1.23-1.53	1.21	1.13-1.29	< .001
Total serum cholesterol (per 40 mg/dL)	1.14	0.92-1.41	1.16	1.04-1.29	1.13	1.06-1.20	.992
Smoke							
Never	1.0	-	1.0	-	1.0	-	
Former	2.49	1.14-5.44	0.80	0.51-1.26	0.96	0.78-1.17	< .001
Current	5.38	2.99-9.67	2.74	2.11-3.56	1.71	1.48-1.97	
Body mass index (per 4 kg/m ²)	1.16	0.97-1.39	1.19	1.08-1.31	1.19	1.12-1.26	.719
Diabetes mellitus	3.84	1.82-8.13	2.55	1.55-4.20	1.60	1.10-2.32	.004
Minor ECG abnormalities	1.11	0.44-2.81	1.51	0.97-2.37	1.06	0.80-1.40	.810
Major ECG abnormalities	1.33	0.74-2.41	1.56	1.15-2.13	1.22	1.01-1.48	.976

^aP value of <.05 suggests that the strength of the association between the risk factor and CVD death was different across the follow-up periods.

CHA indicates Chicago Heart Association Detection Project in Industry; CI = confidence interval; ECG = electrocardiogram; HR = hazard ratio.

of follow-up (>20 years). In contrast, the associated relative risk for BMI is stronger during the later follow-up periods and weaker during the short-term. The associated risk for coronary heart disease events from elevated total serum cholesterol generally remains consistent across different follow-up periods. For systolic blood pressure, most studies suggest that the associated risk appears to diminish. Findings from our study are generally consistent

with these prior reports.

There are several potential mechanisms that might explain the observed differences in associated risk for the major CVD risk factors across different periods of follow-up. First, the association of a risk factor with long-term outcomes depends on risk-factor tracking across time (ie, the risk factor at baseline classifies an individual as “high risk” or “low risk” consistently across time); thus, those risk factors with bet-

ter long-term tracking (eg, BMI) appear to provide more stable estimates across different periods of follow-up compared with those with worse tracking across time (eg, blood pressure).

Second, the strength of traditional CVD risk factors can vary because of the nature of the association between the risk factor and CVD. For example, although the relative risk for BMI increases across increasing duration of follow-up, the relative risk diminishes

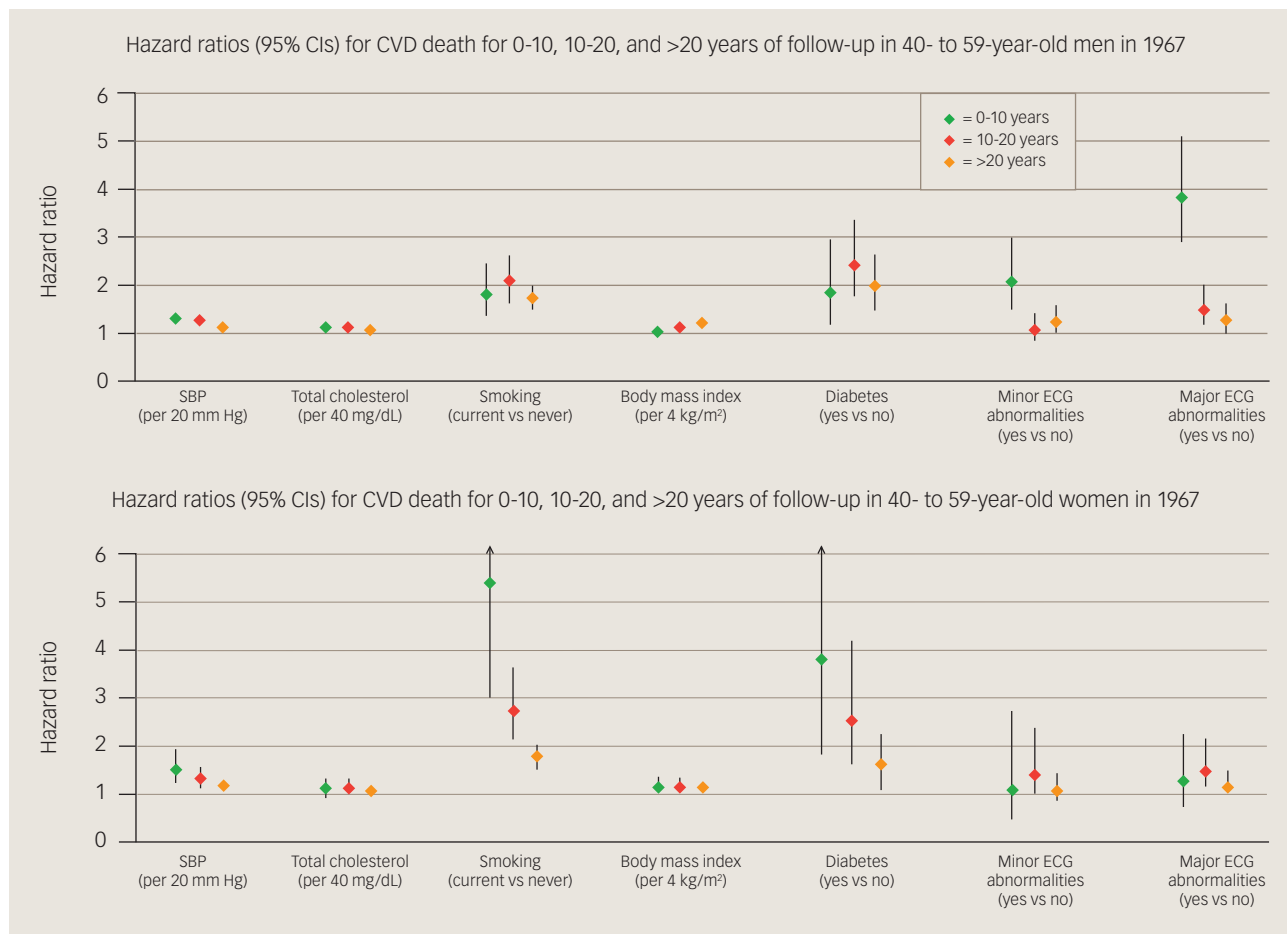


Figure. Multivariable-adjusted relative risks for CVD death during selected periods of follow-up (0-10, 10-20, and >20 years) for different risk factors measured at baseline. All point estimates and 95% CIs reflect multivariable adjustment for all other risk factors. CIs indicates confidence intervals; CVD = cardiovascular disease; ECG = electrocardiogram; SBP = systolic blood pressure.

with adjustment for baseline systolic blood pressure, total cholesterol, and diabetes, suggesting that the risk attributable to BMI is mediated by these risk factors; therefore, a higher BMI at study entry increases the risk for the development of these other risk factors in the future.⁶⁻⁸

Third, risk-factor strength can vary because of competing risk. Several of the traditional CVD risk factors are well-known determinants of both CVD and non-CVD death.^{9,10} For example, smoking increases the risk for death from both CVD and cancer. In CVD survival analyses, individuals who die from a competing cause (eg, cancer) are treated as “censored” observations and removed from the risk set, resulting in an attenuation of the observed hazard ratio for CVD

death.¹¹ As a result, the hazard ratios for CVD death for those risk factors associated with non-CVD death will attenuate more than the risk factors not associated with non-CVD death; thus, the competing risk of non-CVD death associated with systolic blood pressure and smoking likely explains some of the trends observed in previous studies. The finding that the association between total cholesterol and CVD death was unchanged across all follow-up periods in our study is consistent with this interpretation because total cholesterol is generally not associated with non-CVD death.

Treatment effects provide a final explanation for variation in risk-factor strength. Successful treatment strategies for elevated cholesterol levels and high blood pressure have resulted in

substantial decline in population levels of these risk factors over the past several decades.¹² For example, those individuals with the highest blood pressure are more likely to be treated, diminishing their risk over time.

Conclusions

We found some important sex differences in relative risk for several of the traditional risk factors across different periods of follow-up. In women, the greatest increase in risk for CVD death was in the early follow-up period and came from smoking and diabetes mellitus. This finding indicates that women who are diabetic or smoke require a more intensive prevention strategy, including counseling on smoking cessation and risk-factor modification. •

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A more detailed discussion of this topic can be found in Berry JD, Dyer A, Carnethon M, Tian L, Greenland P, Lloyd-Jones DM. Association of traditional risk factors with cardiovascular death across 0 to 10, 10 to 20, and >20 years follow-up in men and women. Am J Cardiol. 2008;101(1):89-94. Tables and Figure reprinted with permission.

Counseling may prove effective in patients with CVD risk factors

A 45-year-old woman presented to our institution for cardiovascular risk assessment. The patient had no personal or family history of cardiovascular disease (CVD), but reported smoking 1 pack of cigarettes daily. She noted exercising occasionally without symptomatic limitations.

On physical examination, the patient appeared to be healthy, despite being overweight (body mass index, 28.7 kg/m²). Her blood pressure was 138/75 mm Hg in both arms, and the

examination was otherwise normal. Laboratory studies revealed a fasting blood glucose of 94 mg/dL, total cholesterol of 185 mg/dL, and high-density lipoprotein cholesterol of 51 mg/dL. Her serum creatinine was normal. A resting electrocardiogram (ECG) showed nonspecific ST-segment and T-wave abnormalities. The presence of these abnormalities did not prompt additional testing because a high proportion of false-positive ECG abnormalities are known to occur in individuals

in the patient's age range.

Although the patient's absolute 10-year risk for coronary heart disease was low, her heavy smoking history was associated with a marked increase in her relative CVD risk in the short-term. The patient noted having significant difficulty in stopping smoking in the past, but an extensive discussion with her regarding the marked short-term risks of smoking in women translated into successful smoking cessation over the next 3 months. •