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THE ASSOCIATION BETWEEN EDUCATIONAL LEVEL AND RISK OF CARDIOVASCULAR DISEASE FATALITY AMONG WOMEN WITH CARDIOVASCULAR DISEASE

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Background: **The inverse relation of socioeconomic status with incident cardiovascular diseases (CVDs) has been well established. However, few data are available describing this relation among ethnically diverse women with prevalent CVD. Using education as a proxy for socioeconomic status, we examined its relation to CVD mortality among women with established CVD.**

Subjects: **Data from 2,157 women with CVD at baseline, who participated in nine long-term U.S. cohort studies, were pooled.**

Methods: **Cox regression models adjusted for history of diabetes mellitus, total cholesterol, systolic and diastolic blood pressure, body mass index, smoking, race/ethnicity, and age at baseline were used to estimate hazard ratios for CVD mortality between non–high school graduates and high school graduates.**

Results: **During a mean follow-up time of 11.5 years, 615 CVD deaths were observed. There was an age-dependent ($p = .003$) inverse association between education and CVD mortality among women with CVD. At age 60, the risk of dying due to CVD among non–high school graduates was more than twice greater than that of high school graduates (hazard ratio = 2.34; 95% CI 1.27–4.29). At age 65, the hazard ratio decreased to 1.31 (95% CI 1.00–1.71). By age 70, there was no difference in the hazard of dying between high school graduates and nongraduates (hazard ratio = 1.01; 95% CI .85–1.21).**

Conclusions: **Our results show that among women with CVD, educational level was a significant, and age-dependent, predictor of fatal CVD independent of other traditional risk factors. These women are an important high-risk population to target secondary prevention and educational efforts.**

Introduction

Socioeconomic status (SES) has been shown to be an independent risk factor for incidence of cardiovascular disease (CVD) since 1960 (Marmot, Shipley, & Rose, 1984; Lynch et al.,. 1996; Diez-Roux et al., 1995). Several studies have found an inverse association between SES and CVD mortality among middle-aged adults (Feldman et al., 1989; Mackenbach et al., 2000; Otten & Bosma, 1997; Salomaa et al., 2000; Shkolnikov et al., 1998). Education is one of the most commonly used proxies for SES (Kaplan & Keil, 1993; Kitagawa & Hauser, 1973) because educational level is simple to collect, is associated with a high response rate, is minimally affected by later health status (reverse causation), and remains relatively constant (Kaplan & Keil, 1993; Kitagawa & Hauser, 1973; Bassuk, Berkman, & Amick, 2002).

Many epidemiological studies have demonstrated the inverse association of education with incident CVD mortality including coronary heart disease (CHD) deaths (Marmot, Shipley, & Rose, 1984; Lynch et al., 1996; Diez-Roux et al., 1995; Feldman et al., 1989; Mackenbach et al., 2000; Otten & Bosma, 1997; Salo-

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maa et al., 2000; Shkolnikov et al., 1998; Kitagawa & Hauser, 1973; Bassuk, Berkman, & Amick, 2002; Elo & Preston, 1996; Hemingway et al., 2000; Mustard et al., 1997; Wamala & Orth-Gomer, 1998; Gonzalez, Rodriguez Artalejo, & Calero, 1998; Tenconi, Devoti, & Comelli, 2000; Liu et al., 1982; Antonovsky, 1967). Gonzalez et al. (1998) and Mackenbach et al. (2000) showed a significant inverse association between education and CVD using internationally pooled data. The inverse association between education and CHD mortality was also shown in middle-aged Italian men (40–69 years; Tenconi, Devoti, & Comelli, 2000) and whites in the United States (40–59 years; Liu et al., 1982). In addition, the protective effect of education on CVD mortality has been demonstrated in large population-based epidemiological studies (Feldman et al., 1989; Otten & Bosma, 1997). In Dutch adults (≥19 years), the protective impact of education on heart disease mortality was more apparent in middle-aged and older people (≥40 years) compared to adults in general (Otten & Bosma, 1997). The inverse association was also shown among U.S. whites aged 45–74 years with a clear dose-response (Feldman et al., 1989). Studies of the relation between education and recurrent CHD are limited.

Several potential mechanisms may explain the association between education and CVD mortality. Education is inversely associated with established CVD risk factors such as blood pressure, lipid levels, and obesity (Feldman et al., 1989; Gran, 1995; Luepker et al., 1993; Garrison et al., 1993; Cirera et al., 1998; Jacobsen & Thelle, 1988; Matthews et al., 1989; Gupta, Gupta, & Ahluwalia, 1994; Pekkanen et al., 1995). In addition, the association between education and CHD may be mediated through psychosocial factors. Psychosocial factors are differentially distributed across education (Hemingway et al., 2000; Wamala et al., 1999). Individuals with low educational levels tend to have jobs with low responsibility and high demand, which may increase stress levels. Release of stress hormones could alter hemodynamics, lipid metabolism, homeostasis, and other factors, increasing susceptibility to CVD (Feldman et al., 1989; Hemingway et al., 2000; Wamala et al., 1999). Lastly, education as a proxy for SES may be related to access to medical care (Feldman et al., 1989).

Most studies of educational level and CVD have been limited to populations free of CVD at baseline (Feldman et al., 1989; Mackenbach et al., 2000; Otten & Bosma, 1997; Salomaa et al., 2000; Shkolnikov et al., 1998; Bassuk, Berkman, & Amick, 2002). Few data have estimated this relation in women with prevalent CVD. The purpose of this study was to evaluate the relation between education and CVD mortality among ethnically diverse adult women with CVD and to determine if differences in traditional risk factors explain any difference in CVD mortality based on educational status. Prevalent CVD, in this study, was composed of a history of CHD, defined by a baseline record of angina and/or myocardial infarction (MI), and/or a history of stroke at baseline according to cohort-specific definitions and their diagnostic criteria (Appendix 1).

Methods

Study sample

Data were from the Women's Pooling Project (WPP), which is the combined data from nine U.S. population-based prospective cohort studies (Atherosclerosis Risk in Communities Study [ARIC], Charleston Heart Study, Evans County Study, Framingham Heart Study, Framingham Offspring Study, National Health and Nutrition Examination Survey Epidemiologic Follow-up Study [NHEFS], Rancho Bernardo Study, San Antonio Heart Study, and Tecumseh Community Health Study). Details of sampling procedures, study designs, and methods for each cohort have been published elsewhere (The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives, 1989; Jackson et al., 1996; National Heart, Lung and Blood Institute, 1987; Bolye, 1970; Keil et al., 1984; Johnson et al., 1986; McDonough et al., 1965; Gordon & Shurtleff, 1973; Cohen et al., 1987; National Center for Health Statistics, 1973; Criqui, Barrett-Connor, & Austin, 1978; Hazuda et al., 1986; Epstein et al., 1965). The sample included in this analysis includes 2,157 women with CVD. Women were included in this study if at baseline they were 30 years or older with prevalent CVD and had data available on history of diabetes, blood pressure, total cholesterol, smoking status, height, and weight.

Definitions of baseline variables

Educational attainment for each subject was dichotomized as high school graduate or not. This was done because high school graduate was available in all cohorts. All cohorts defined subject completion of 12 years of education as a high school graduate except for the Charleston and Evans county studies, where 11 years was required for high school graduation. History of diabetes was identified by serum glucose level or treatment in all cohorts except NHEFS and Charleston study, which used self-reported physician diagnosis, and ARIC study, which combined both criteria. Smoking was classified as current smoker or not. Nonsmokers included those who never or formerly smoked. Baseline age and race/ethnicity were assessed by cohort-specific questionnaires. Total cholesterol was measured according to cohort-specific methods. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were assessed as the mean of the last two readings unless only one reading was available, in which case the single reading was used. Body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared.

Assessment of CVD death

CVD mortality was identified based on the International Classification of Disease (ICD) codes 401-448 (National Center for Health Statistics, 1967; World Health Organization, 1977). Most of the studies used ICD code version 9, except the Charleston, Evans County, and Framingham studies whose baseline examination were done in the 1960s and used ICD code version 8.

Statistical analysis

Baseline characteristics of high school graduates and non–high school graduates were compared using χ^2 tests for categorical variables and two-sided *t*-tests for continuous variables. A p value $<.05$ was considered significant.

To examine the association between educational level and age with CVD mortality, Cox regression models using age as the time axis with left truncation at baseline age were used (Allison, 1995). Women not recorded as dying from CVD were treated as censored on the last day recorded alive. First, Cox proportional hazards regression models were used to estimate age-specific hazard ratios (HR) of non–high school graduates to high school graduates for the midpoint (N) of 5-year intervals. Each group included all women who participated in the study during the 5-year interval age group N $\pm$ 2.5 years. Events that occurred after this interval were treated as censored at the end of the interval.

Next we used nonproportional hazards regression models by introducing an interaction term between age and educational status in Cox models to account for the age-dependent effect of education on CVD mortality risk. The addition of an interaction between education and age in the model allowed us to calculate the age-specific effect of education on CVD fatality continuously. The nonproportional regression model was restricted to age groups N = 60 to N = 90 years, because of the small number of CVD deaths (<30 events) in the extreme age groups (N $\leq$ 55 years and N $\geq$ 95 years). The -2 log likelihood ratio statistic, a measure of model agreement with data, was used to identify the best-fitted nonproportional Cox regression model (Collett, 1994). The significance of the interaction term was determined by the difference between the -2 log likelihood (which has a χ^2 distribution with 1 degree of freedom) in models before and after the interaction term was added. Both baseline age-adjusted HR and adjusted HR (controlled for history of diabetes, total cholesterol, SBP, DBP, BMI, smoking and race/ethnicity, in addition to baseline age) were calculated for both proportional and nonproportional hazards regression models. To identify the significance of association, the HR and its 95% confidence interval (CI) were used. When the 95% CI did not include 1, it was considered significant.

Lastly, secondary analyses were done to examine potential cohort effects on the association using stratification in the nonproportional regression model (Collett, 1994). Also, general trends of the relationship between education and CVD mortality in women with CVD were explored in each cohort individually to identify any specific cohort influence on the overall pattern of the association. Cohorts with less than 5% of CVD deaths in the age groups between N = 60 and N = 90 years were excluded for this analysis (Charleston Heart Study, Evans County Study, Framingham Offspring, and San Antonio Heart Study) because of their small number of events. All analyses were done using SAS version 8.01 (SAS Institute Inc., 1999).

Results

Table 1 describes baseline characteristics of 2,157 women with established CVD by educational status. During a mean follow-up of 11.5 $\pm$ 7.4 years (24,863 person-time years), 615 CVD deaths were observed. High school graduates, compared to non–high school graduates, were younger (57 $\pm$ 9 versus 59 $\pm$ 10 years; $p < .0001$), were less likely to be diabetic (12% versus 18%; $p < .0001$), and had lower means for traditional risk factors: total cholesterol (6.09 $\pm$ 1.27 versus 6.28 $\pm$ 1.28 mmol/L; $p = .0007$), SBP (135 $\pm$ 28 versus 146 $\pm$ 31 mm Hg; $p < .0001$), DBP (79 $\pm$ 15 versus 84 $\pm$ 16 mm Hg; $p < .0001$), and BMI (27 $\pm$ 6 versus 29 $\pm$ 7 kg/m^2; $p < .0001$). Moreover, the distribution of race/ethnicity between high school graduates and nongraduates were significantly different ($p < .0001$); specifically, high school graduates were more likely to be white (86% versus 70%; $p < .0001$).

Age-specific HR from Cox proportional hazards regression models, adjusted for baseline age and traditional risk factors (total cholesterol, SBP, DBP, history of diabetes, BMI, smoking status, and race/ethnicity) in addition to baseline age, are shown in Table 2. The age-specific effect was calculated in each 5-year interval age group as an estimate for the HR of the midpoint (N) in each group. The association between education and CVD fatality was greatest in age group N = 60 in both age-adjusted (HR = 2.16; 95% CI 1.09–4.27) and fully adjusted models (HR = 2.11; 95% CI 1.03–4.33). But, it became not very different from a hazard ratio of 1 by age group N = 70.

We next modeled the change in association between education and CVD fatality in a continuous manner using an interaction term between education and age in a Cox nonproportional hazards model. Because few CVD deaths (<30 events) occurred in the extreme age

Table 1. Baseline characteristics among women with cardiovascular disease

	Non-HS Graduate (n = 1027)	HS Graduate (n = 1130)	p value
Baseline age (years) (mean ± SD)	59 ±10	57 ±9	<.0001
≥65 years, n (%)	335 (33)	226 (20)	<.0001
Race/ethnicity			
White, n (%)	723 (70)	971 (86)	
Black, n (%)	212 (21)	123 (10.9)	
Hispanic, n (%)	89 (8.7)	35 (3)	
Other, n (%)	3 (0.3)	1 (0.1)	<.0001[a]
Disease history			
Coronary heart disease, n (%)	804 (84)	915 (86)	.28
Stroke, n (%)	300 (30)	289 (26)	.037
Diabetes mellitus, n (%)	186 (18)	136 (12)	<.0001
Cholesterol (mmol/L) (mean ± SD)	6.28 ±1.28	6.09 ±1.27	.0007
SBP (mm Hg) (mean ± SD)	146 ±31	135 ±28	<.0001
DBP (mm Hg) (mean ± SD)	84 ±16	79 ±15	<.0001
BMI (kg/m^2) (mean ± SD)	29 ±7	27 ±6	<.0001
Smoker, n (%)	286 (28)	301 (27)	.53

Abbreviations: HS, high school; SD, standard deviation; CHD, coronary heart disease; SBP, systolic blood pressure, DBP, diastolic blood pressure; BMI, body mass index.
[a]The proportion of race/ethnicity between HS graduates and non-HS graduates.

groups (N ≤ 55 and N ≥ 95 years), the analysis was restricted to age groups N = 60 to N = 90 years. The decrease in the −2 log likelihood statistics was significant (χ^2 = 9.3 with 1 degree of freedom; p = .002) when the interaction term was included. Therefore, we used the nonproportional hazards model to identify a continuous association between education and CVD fatality in women with CVD. The inverse association of education with CVD fatality in women with established CVD was summarized using both proportional and nonproportional models, adjusted for traditional risk factors in age groups N = 60 to N = 90 years in Figure 1. The nonproportional Cox regression model (solid line) with its 95% CI (dotted line) shows the continuous change of the effect of education on CVD mortality with age, while the results of the proportional model, for each 5-year age group, is represented by solid circles for each midpoint N. The inverse association of education with CVD mortality among women with CVD was age-dependent. In the continuous model, non–high school graduates had 2.34 times higher risk of dying due to CVD than high school graduates (95% CI 1.27–4.29) at age 60 years. By age 65 years the hazard ratio decreased to 1.31 (95% CI 1.00–1.71), and by age 70 years, the risk of dying due to CVD was similar for non–high school graduates and high school graduates (HR = 1.01; 95% CI .85–1.21). These results remained similar when

Table 2. Age-specific cardiovascular disease mortality hazard ratios of non–high school graduates to high school graduates among women with cardiovascular disease at baseline

Age Group (N[a])	CVD Deaths	Number of Subjects	HR (95% CI)[b]	HR (95% CI)[c]
45	2	263	—	—
50	10	567	1.04 (0.29–3.69)	0.80 (0.21–2.99)
55	17	884	0.81 (0.30–2.19)	0.64 (0.23–1.75)
60	36	1087	2.16 (1.09–4.27)	2.11 (1.03–4.33)
65	47	1146	1.85 (1.02–3.36)	1.76 (0.94–3.29)
70	86	1070	1.05 (0.69–1.61)	0.97 (0.62–1.52)
75	107	808	1.00 (0.68–1.47)	0.91 (0.61–1.37)
80	126	604	0.95 (0.67–1.35)	0.89 (0.61–1.30)
85	106	372	0.76 (0.52–1.12)	0.71 (0.47–1.07)
90	57	159	0.97 (0.57–1.65)	0.88 (0.49–1.60)
95	18	36	0.84 (0.33–2.14)	0.74 (0.24–2.26)
100	3	4	—	—

Abbreviations: CVD, cardiovascular disease; HR, hazards ratio; CI, confidence interval.
[a]Age group N included all women who participated in the study during the 5-year interval N ± 2.5 years. Events that occurred after the interval were treated as censored at the end of the interval.
[b]Baseline age-adjusted hazard ratio.
[c]Hazard ratio adjusted for age at baseline, history of diabetes mellitus, total cholesterol, systolic and diastolic blood pressure, body mass index, smoking status, and race/ethnicity.

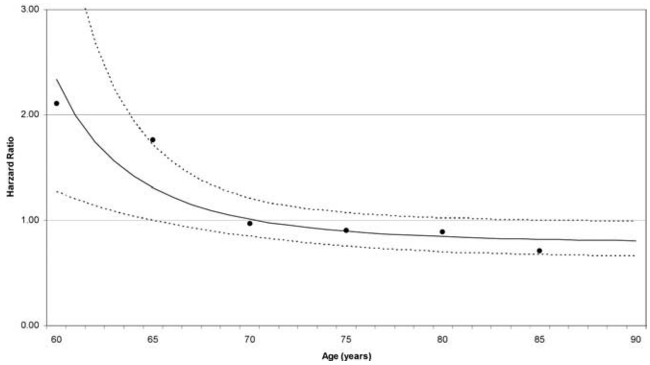

Figure 1. Adjusted age-specific cardiovascular disease mortality hazard ratios of non–high school graduates to high school graduates among women with cardiovascular disease. Hazard ratios calculated from Cox regression models adjusted for baseline age, history of diabetes mellitus, body mass index, total cholesterol, systolic and diastolic blood pressure, smoking status, and race/ethnicity at baseline. Continuous line derived from nonproportional hazards model containing an interaction term between education and age. Dotted line represents the 95% confidence interval for nonproportional hazards model. Solid circles derived from proportional hazards models for the midpoint (N) in 5-year interval age groups.

women with angina only (n = 948) were excluded, with hazard ratios of 3.03, 1.27, and .86 for ages 60, 65, and 70, respectively (p = .0021 for the inclusion of the interaction term).

The potential cohort effects on the association of education with CVD fatality among women with CVD were examined using stratification in the nonproportional Cox regression model. The inverse relationship between education and CVD mortality remained significant (p = .02). In addition, we examined the association in each cohort individually to identify any specific cohort influence on the overall trend. Each cohort had similar patterns of the inverse association (see Appendix 2 and Figure 2). The significant age-dependent inverse relationship of education with CVD fatality among women with CVD seems to be determined by the general trend of association in this study, not due to cohort effects.

Discussion

This is one of the first studies to determine the association between education and CVD fatality among women with CVD. In this study, there was a significant interaction between education and age in predicting CVD mortality, with high school graduates showing a protective effect at age 60 years that decreased and disappeared by age 70 years. The age-dependent inverse association between education and CVD mortality persisted across race/ethnicity.

Recently, two studies showed a significant inverse association of SES with CHD mortality regardless of baseline disease status (Salomaa et al., 2000; Hemingway et al., 2000). First, Hemingway et al. (2000) identified the inverse association between occupational gradient and CHD mortality among middle-aged (40–69 years) British civil servants. This study demonstrated that the inverse association was more significant among civil servants without CHD at baseline than those with. The risk of CHD mortality in the lowest grade of occupation was increased by 72% (95% CI 1.4–2.1) compared to that in the highest among men without CHD, while the increase was 56% (95% CI 1.1–2.1) among those with CHD. In addition, Salomaa et al. (2000) confirmed the finding from Hemingway et al. (2000) using the data from the Finnish contribution to the World Health Organization (WHO) multinational monitoring of trends and determinants of cardiovascular disease (FINMONICA) MI registry during 1983–1992. Among middle-aged (35–64 years) Finnish adults, there was a significant inverse association between education and MI death, regardless of prevalence of MI. In contrast to Hemingway et al. (2000), the protective effect of education in this study was more significant among people with MI than without across gender. Furthermore, this study showed that the protective effect of education on MI case-fatality was much stronger in women than in men. Less-educated men had 87% higher risk for a 1-year case-fatality than high-educated men (95% CI 1.71–2.05), while the risk in less-educated women was increased by 134% compared to the risk among high-educated women (95% CI 1.88–2.92).

Our data are consistent with other studies showing that the impact of education on CVD mortality is age-dependent. Antonovsky et al. (1967) evaluated

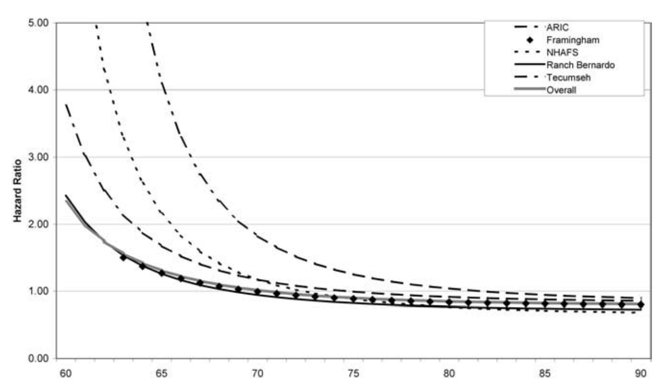

Figure 2. General trends of the association between educational level and cardiovascular disease mortality among women with cardiovascular disease across cohorts. Six lines including overall trend derived from cohort-specific nonproportional hazard models containing an interaction term between education and age and adjusted for baseline age, history of diabetes mellitus, body mass index, total cholesterol, systolic and diastolic blood pressure, smoking status, and race/ethnicity at baseline.

that the impact of SES on health was most prominent in young and middle-aged adults. In addition, the impact disappeared with advancing age (aged ≥70 years), regardless of race/ethnicity. The decrease in the hazard ratio of education with advanced age may be due to the increasing relative importance of the background rate of CVD and other risk factors.

Relative risk peaked at aged 30–44 years, then started declining and disappeared at age 65 years and older. Also, the inverse association has been found among the middle-aged and then disappeared after age 65 years (Elo & Preston, 1996; Mustard et al., 1997; Kitagawa & Hauser, 1973). But a recent study showed that the protective effect of education on overall mortality persisted beyond middle-age, even though the strength of association was weaker than that in middle-aged (Bassuk, Berkman, & Amick, 2002). Community-living elderly men (aged ≥65 years) with low education (≤7 years) had 44% increased risk of dying, compared to those with the highest (≥13 years) (95% CI 1.07–1.94).

Study strength and limitations

Although our dataset had several advantages, compared to previous studies, which allowed us to identify the association of education with CVD fatality among adult women with CVD and to test the significance of the interaction between education and age among them, there were also several limitations. Due to the small number of CVD deaths (<30 events) in the youngest and oldest age groups (N ≤ 55 and N ≥ 95 years), they were not included in this analysis. Measurement errors due to differences in methodologies between cohorts might have biased our results, but when data were examined within cohorts, the results were similar. Lastly, although commonly used, education may not be a good proxy for SES.

Conclusions

We found that an inverse association between educational level and CVD mortality is evident among women with prevalent CVD. Moreover, there was a significant interaction between education and age among women with CVD. The inverse association between educational level and CVD mortality was greatest in women at age 60 years, decreased with age, and disappeared by age 70 years. Considering that women have higher prevalence of CVD and CVD case-fatality than men with increasing age (≥65 years; American Heart Association, 2003; Lerner & Kannel, 1986; Marrugat et al, 2001; Vaccarino, Berkman, & Krumholz, 2000), the significant protective effect of education from our study might give a novel strategy to reduce CVD mortality among women with CVD. Especially for middle-aged women with low education, increasing heart health education program may improve their awareness of CVD risk and then result in modifying lifestyle change by continuous education, which further leads to decrease CVD mortality gap between high school graduate and non–high school graduate among middle-aged women. More intensive preventive and educational efforts may be needed to target less-educated women across race/ethnicity by health professionals and public health policy makers to maximize survival from CVD in women. This may include an emphasis on blood pressure, blood lipid, and weight control. In addition, more studies are needed to identify this association across race/ethnicity among adult women.

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Appendix 1. Diagnostic criteria for history of MI, angina, and stroke in each cohort

Cohort	Previous MI	Previous Angina	Previous Stroke
ARIC	ECG evidence and medical history	Rose questionnaire	Doctor's diagnosis, "Has a doctor ever told you had stroke?"
Charleston	Self-reported history and ECG evidence	Self-reported history	NA
Evans' County	Review panel	Review panel	Review panel
Framingham	Review panel	Chest pain questionnaire and review panel	Physician or hospital record
NHEFS	Self reported, "Have a doctor ever told you—?"	NA	Doctor's diagnosis, "Has a doctor told that you had condition"
Framingham Offspring	Same method as Framingham		Same method as Framingham
Rancho Bernado	Self-reported, "Have you ever been hospitalized for a heart attack?" and review panel validated the results	NA	Self-reported, "Have you ever had a stroke?"
San Antonio	Self-reported, "Has a doctor ever told you—" or Minnesota-coded ECG	Rose questionnaire	Self-reported stroke
Tecumseh	Self-reported, "Has a doctor ever told you had a heart attack?" or diagnosis from interview data or ECG	Chest pain questionnaire and review panel	Self-reported, "Have you ever had a stroke?"

Abbreviations: MI, myocardial infarction; ECG, electrocardiogram; NA, not applicable.

Appendix 2

Assessing general patterns of the association across cohorts

General trends of the inverse association between educational level and CVD fatality in women with CVD were examined to identify any specific cohort influence on the overall pattern (Figure 2). Cohorts with at least 5% of CVD deaths in the age groups N = 60 to N = 90 years (ARIC, NHEFS, Rancho Bernardo, and Tecumseh studies) were included in this analysis, except for the Framingham study, which only included N = 65 to N = 90 years because of the small number of events in the age group N = 60 years (7/247 = 2.8%). Nonproportional hazard models containing an interaction term between education and age derived from each cohort including overall trend and adjusted for baseline age, history of diabetes mellitus, body mass index, total cholesterol, systolic and diastolic blood pressure, smoking status, and race/ethnicity at baseline. All five cohorts had similar patterns of the inverse association between education and CVD fatality and the variance of curvature in each cohort might be due to their different events and sample sizes in any given age.

In conclusion, the overall nonproportional hazard model seems to well illustrate the general pattern of the relationship of education with CVD fatality among women with CVD in our study, not due to the any specific cohort influence.

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