

# The Gender Gap in Coronary Heart Disease Mortality: Is There a Difference between Blacks and Whites?

Data from the U.S. Cohorts Pooling Project

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## ABSTRACT

**Background:** The gender difference (gender gap) in mortality due to coronary heart disease (CHD) decreases with age. This relationship has not been well characterized in diverse populations.

**Methods:** To examine the gender gap in CHD mortality across age groups and to compare the age dependency of the gender gap between blacks and whites, we conducted a prospective cohort study combining data from 9 U.S. epidemiological studies (Atherosclerosis Risk in Communities Study [ARIC], Charleston Heart Study, Evans County Study, Framingham Heart Study [original and offspring cohorts], National Health Examination Follow-up Study [NHEFS], Rancho Bernardo Study, San Antonio Heart Study, and Tecumseh Community Health Study). Baseline examinations were performed between 1958 and 1990 (depending on the study), and mean follow-up was 13.7 years in general communities in several U.S. geographic areas. We included 39,614 subjects >30 years and free of cardiovascular disease (CVD) at baseline (18% blacks, 37% men). Completion of follow-up was >97% for all studies. As the main outcome measures, age-specific CHD mortality rates and male/female CHD mortality hazard ratios were calculated using Cox hazards regression.

**Results:** During 542,605 person-years of follow-up, 2,812 CHD deaths were observed (18% in blacks, 46% in men). At age 45, white men were at a 6-fold increased risk compared with white women (95% confidence interval [95% CI] 4.6–7.9), whereas black men had a 2-fold increased risk of fatal CHD compared with black women (1.4–3.6). At age 95, men and women were at equal risk in both whites (0.9–1.4) and blacks (0.7–1.6). The difference in the age dependency of the gender gap between blacks and whites was significant ( $p < 0.0001$ ).

**Conclusions:** The gender difference in CHD mortality was more pronounced in whites than in blacks at younger ages. This discrepancy was not explained by adjustment for CHD risk factors and suggests that other factors may be responsible for the ethnic variation in the gender gap.

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## INTRODUCTION

ALTHOUGH CORONARY HEART DISEASE (CHD) is the leading cause of death in men and women, age-specific CHD mortality rates are strikingly higher in men compared with women.<sup>1</sup> In general, both CHD incidence and mortality rates in women lag 10 years behind those of men.<sup>2</sup> It is well established that the gender difference is more pronounced at younger ages, such that 1 in 17 women has had a coronary event before age 60, in contrast with 1 in 5 men. The gender difference has been reported to decrease with age, and after age 60, CHD accounts for 1 in 4 deaths in both sexes<sup>3</sup> (Table 1).

Previous U.S.-based studies addressing gender differences in CHD mortality have been limited to predominantly Caucasian populations.<sup>4-6</sup> Many studies have also examined black and white differences in CHD mortality, but none has directly compared the gender gap between ethnic groups.<sup>7-14</sup>

The gender gap in CHD mortality has been attributed to various factors. Differential prevalence and impact of traditional cardiovascular risk factors have been shown to account for part but not all of the gender difference.<sup>15,16</sup> Estrogen has been implicated as a possible protective factor in women because of an observed 2-fold increased CHD incidence in surgically postmenopausal vs. premenopausal women of the same age.<sup>17</sup> However, the use of hormone replacement therapy (HRT) has not been shown to reduce CHD events in postmenopausal women,<sup>18</sup> and

the role of endogenous estrogen in the cardio-protection of women compared with men is not completely understood. International data suggest that geography, secular trends, and environmental factors also play a role in gender differences in CHD occurrence.<sup>11</sup>

The purpose of this study was to examine the relation between age and gender differences in CHD mortality and to compare the age dependency of the gender gap between blacks and whites in more than 39,000 persons who participated in the long-term epidemiological studies included in the U.S. Cohorts Pooling Project. In addition, we sought to determine if adjustment for traditional cardiovascular risk factors attenuated gender differences in CHD mortality.

## MATERIALS AND METHODS

The U.S. Cohorts Pooling Project is a prospective study that combines data from the following nine long-term epidemiological studies based in the United States: Atherosclerosis Risk in Communities Study (ARIC), Charleston Heart Study, Evans County Study, Framingham Heart Study (original and offspring cohort), National Health Examination Follow-up Study (NHEFS), Rancho Bernardo Study, San Antonio Heart Study, and the Tecumseh Community Health Study. Details of sampling procedures, study designs, and methods for each of the respective studies have been described.<sup>7,9,19-29</sup>

TABLE 1. AGE-SPECIFIC CHD MORTALITY FOR WHITES AND BLACKS

Age group (years)	Whites				Blacks			
	Men		Women		Men		Women	
	No. of CHD deaths (PY <sup>a</sup> of follow-up)	Mortality rate (per 1000 PY)	No. of CHD deaths (PY of follow-up)	Mortality rate (per 1000 PY)	No. of CHD deaths (PY of follow-up)	Mortality rate (per 1000 PY)	No. of CHD deaths (PY of follow-up)	Mortality rate (per 1000 PY)
45-50	34 (17,957)	1.9	6 (35,265)	0.2	10 (3,627)	2.8	3 (6,787)	0.4
50-55	62 (24,106)	2.6	23 (44,465)	0.5	14 (5,413)	2.6	14 (9,223)	1.5
55-60	75 (24,244)	3.1	45 (43,519)	1.0	24 (5,211)	4.6	16 (8,399)	1.9
60-65	116 (22,122)	5.2	66 (40,313)	1.6	32 (4,915)	6.5	33 (7,220)	4.6
65-70	139 (17,001)	8.2	95 (35,305)	2.7	29 (4,010)	7.2	32 (5,437)	5.9
70-75	169 (11,549)	14.6	179 (29,282)	6.1	47 (2,768)	17.0	46 (3,827)	12.0
75-80	195 (7,716)	25.3	279 (22,013)	12.7	41 (1,753)	23.4	42 (2,716)	15.5
80-85	146 (3,968)	36.8	270 (13,131)	20.6	35 (830)	42.2	43 (1,530)	28.1
85-90	68 (13,310)	51.9	205 (5,469)	37.5	8 (321)	24.9	22 (591)	37.2
90-95	22 (213)	103.3	79 (1,169)	67.6	5 (68)	73.0	7 (156)	44.8

<sup>a</sup>PY, person-years.

All subjects were 30 years or older and had no cardiovascular disease (CVD) at initial examination. CVD was defined as a history of angina, myocardial infarction (MI), or stroke as specified by each cohort. Subject variables measured at baseline included total cholesterol, blood pressure, body mass index (BMI), smoking status, prevalent diabetes mellitus, and education. Both systolic and diastolic blood pressures were recorded as the average of the last two readings unless only one reading was available. BMI ( $\text{kg}/\text{m}^2$ ) was calculated from the raw data for height and weight, and smoking status was stratified according to current and noncurrent cigarette smokers. Prevalent diabetes mellitus was defined by glucose parameters (both serum glucose and oral glucose tolerance tests) or treatment in all cohorts except NHEFS and the Charleston Heart Study, which used self-reported history of physician diagnosis, and ARIC, which used a combination of these criteria. Educational status was dichotomized into non-high school graduate vs. high school graduate. Because of a limited number of deaths in other ethnic groups, only non-Hispanic whites and non-Hispanic blacks (subsequently referred to as whites and blacks) were included in this analysis.

Completion of follow-up was  $>97\%$  for all studies. Mortality data were based on version 9 of the International Classification of Diseases (ICD), except in Charleston, Evans County, and Framingham original and offspring cohorts, which were based on version 8. Primary outcome was CHD mortality, which included acute and old MI, angina pectoris, and other acute, subacute, and chronic forms of ischemic heart disease (ICD-9 code 429.2, ICD-8 code 410, and 410-414 for both versions).<sup>30,31</sup>

### *Statistical analysis*

Baseline characteristics between gender/ethnic groups were compared using Pearson's chi-square tests for dichotomized variables, and two-tailed Student's *t* tests or Wilcoxon rank sum tests for continuous variables.

Mortality rates for each gender/ethnic group were calculated in 5-year age intervals by taking the number of CHD deaths that occurred in a given age stratum (i.e., the age at event or death) and dividing by the total number of person-years of observation and were expressed as the number of events per 1000 person-years.

Ethnicity-specific Cox proportional hazards regression models were then performed using gender in the model to calculate age-specific CHD mortality hazards ratios (HR) between men and women. A separate calculation for each 5-year age group was done.

To account for nonproportional hazard (one that changes with age), a time-dependent covariate was introduced in the model to represent the interaction of gender with age at event.<sup>32,33</sup> This allowed the effect of gender on CHD mortality to change continuously with age and incorporated all data into one model instead of stratifying data into age groups, as was done for proportional hazards calculations. As there were few CHD deaths in the extreme age categories ( $<45$  and  $>95$  years), these ages were used as cutoff points for the nonproportional model calculations. CHD deaths before age 45 were excluded entirely from the model, whereas subjects living past the age of 95 were censored at 95. All deaths due to other causes were censored. Age was used as the time axis in the model, with left truncation to adjust for baseline age. Using the nonproportional hazards regression parameters, age-specific male/female HRs and corresponding 95% confidence intervals (CI) for ages 45–95 were calculated. In addition, black/white HRs for same-sex groups were calculated using nonproportional hazards regression.

To test the relationship between age and gender HRs, the difference in the  $-2$  log likelihood statistic with the addition of the time-dependent covariate into the model was used. A model including both whites and blacks was used to test for statistically significant ethnic differences in the variation of the gender gap with age. The difference in the  $-2$  log likelihood statistic (with the addition of ethnicity into the model), which has a chi-square distribution, was used to calculate *p* values.

Analyses were done for unadjusted data and repeated with adjustment for cholesterol, diastolic and systolic blood pressure, age, and BMI as continuous variables, as well as smoking status, diabetes, educational status, blood pressure medications, and cohort as categorical variables. Subjects with any missing data from risk factor variables were excluded from the adjusted analyses.

Secondary analyses to test for a possible time period effect included stratification of cohorts into decades of baseline examinations (1960s, 1970s, and 1980s), as well as grouping subjects by

decade of birth year. Study baseline examinations were conducted within a 1–7-year span, and entry ages were subtracted from the calendar year at the midpoint of each study entry period to approximate actual birth dates.

Because varying lengths of time between measurement of risk factors and incidence of death could systematically bias results, analyses with a fixed follow-up time were performed. Subjects were censored 10 years after entry to restrict outcomes to those occurring within 10 years of baseline examination. Separate analyses were also done using individual cohorts and excluding cohorts with <10% black populations to account for the possible confounding effect of different study cohorts and geography.

All analyses were performed using SAS version 8.2, and Cox regression models and non-proportional hazard regression models were constructed using the Proc PHREG program.

## RESULTS

The study included a total of 39,614 subjects who were free of CVD at baseline (18.1% blacks, 37.2% men) with mean age  $52.2 \pm 10.9$  years. Characteristics of the participants are listed in Table 2. All risk factor levels were statistically different between men and women (both blacks and whites), with the exception of blood pressure medication use, which was similar in white men and women, and systolic blood pressure, which

was similar in black men and women. Within each sex, risk factors were statistically different between blacks and whites, with the exception of age in both sexes and BMI in men. Compared with whites, blacks had higher blood pressures and higher prevalence of diabetes and were less likely to have graduated from high school.

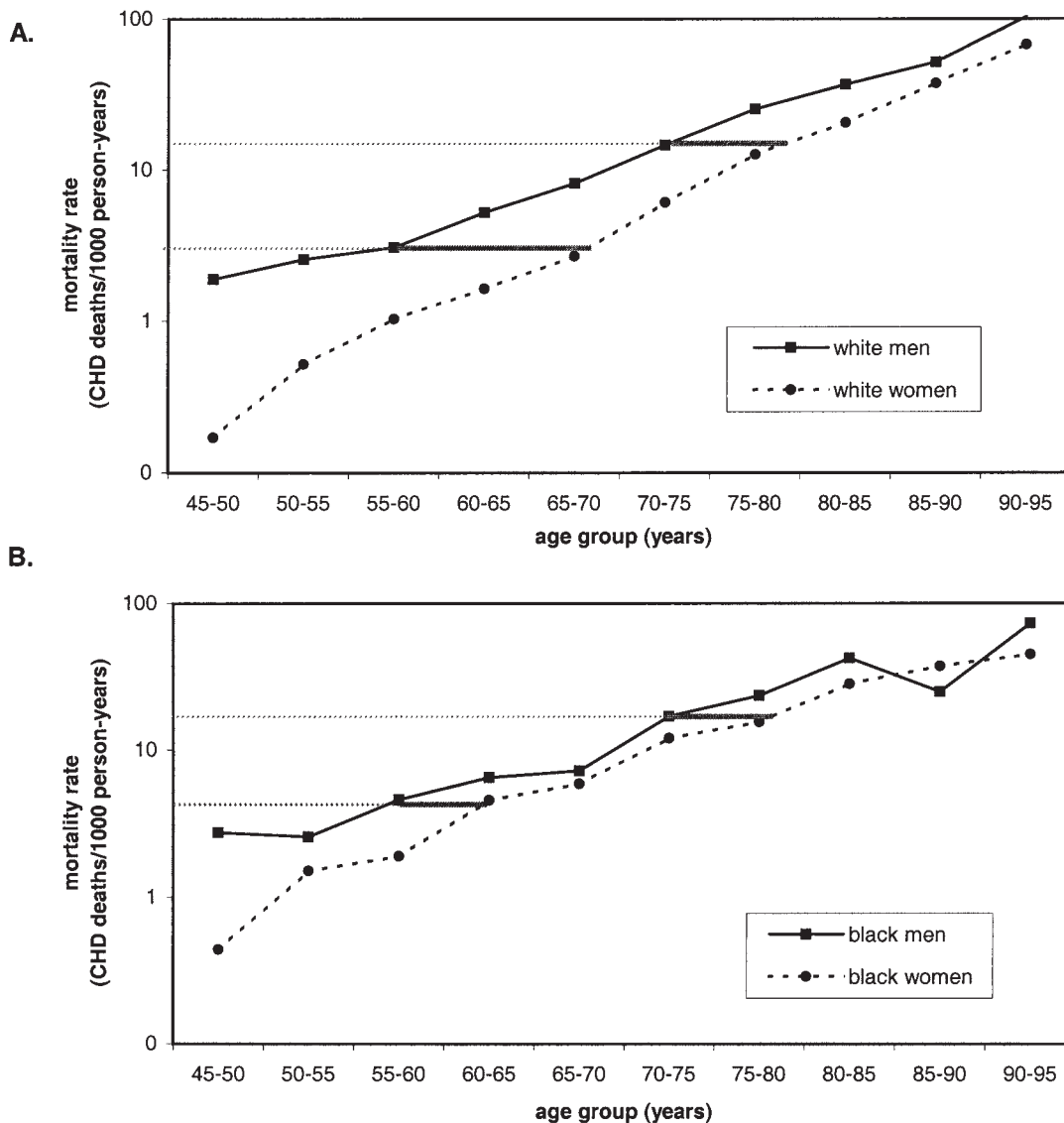
During a total of 542,605 person-years of follow-up (mean  $13.7 \pm 7.8$  years), 2812 CHD deaths were observed (18.1% in blacks, 45.7% in men). Age-specific mortality rates (CHD deaths/1000 person-years) are shown as semi-log graphs for both whites and blacks (Fig. 1). Rates increased dramatically with age in all four gender/ethnic groups, and in both blacks and whites, women had lower CHD mortality rates compared with men in most age groups. CHD mortality rates of white women lagged behind those of white men by 10–15 years in the younger age groups and by 5–10 years in the older age groups. In blacks, the lag time between CHD mortality rates in women and men was 5–10 years in most age groups.

Unadjusted CHD mortality HRs between men and women are shown for whites and blacks in Figure 2. HRs calculated from the proportional hazards model are represented by a data point for each 5-year age stratum. White men were at 7-fold increased risk compared with white women in the 45-year age group (includes subjects aged 42.5–47.5), which decreased to a 3.5-fold increased risk in the 65-year group, and the risk of women approached that of men in the older age groups. HRs calculated from the nonproportional

TABLE 2. DISTRIBUTION OF INDIVIDUAL MAJOR RISK FACTORS AND OTHER CHARACTERISTICS AT BASELINE BY GENDER AND ETHNICITY

Variable	Whites			Blacks		
	Men (n = 11,916)	Women (n = 20,514)	p value	Men (n = 2,820)	Women (n = 4,364)	p value
Serum cholesterol (mmol/L) <sup>a</sup>	5.6 (1.1)	5.8 (1.2)	<0.0001	5.5 (1.2)	5.7 (1.2)	<0.0001
BMI (kg/m <sup>2</sup> )	26 (4)	25 (5)	<0.0001	26 (5)	29 (7)	<0.0001
Systolic BP (mm Hg)	130 (21)	128 (24)	<0.0001	140 (28)	139 (31)	0.13
Diastolic BP (mm Hg)	80 (12)	78 (13)	<0.0001	88 (16)	85 (16)	<0.0001
Age (years)	52 (11)	52 (11)	<0.0001	53 (10)	51 (10)	<0.0001
Follow-up (years)	12.6 (7.6)	15.1 (7.5)	<0.0001	11.1 (8.1)	11.8 (8.3)	<0.0001
Current smoker (%yes)	37	30	<0.0001	45	27	<0.0001
Current BP medications (% yes)	13	13	0.74	19	27	<0.0001
Diabetes (%yes)	6	5	<0.0001	9	13	<0.0001
Education (% less than high school)	35	28	<0.0001	64	57	<0.0001

<sup>a</sup>To convert millimoles per liter to milligrams per deciliter, divide millimoles per liter by 0.02586.

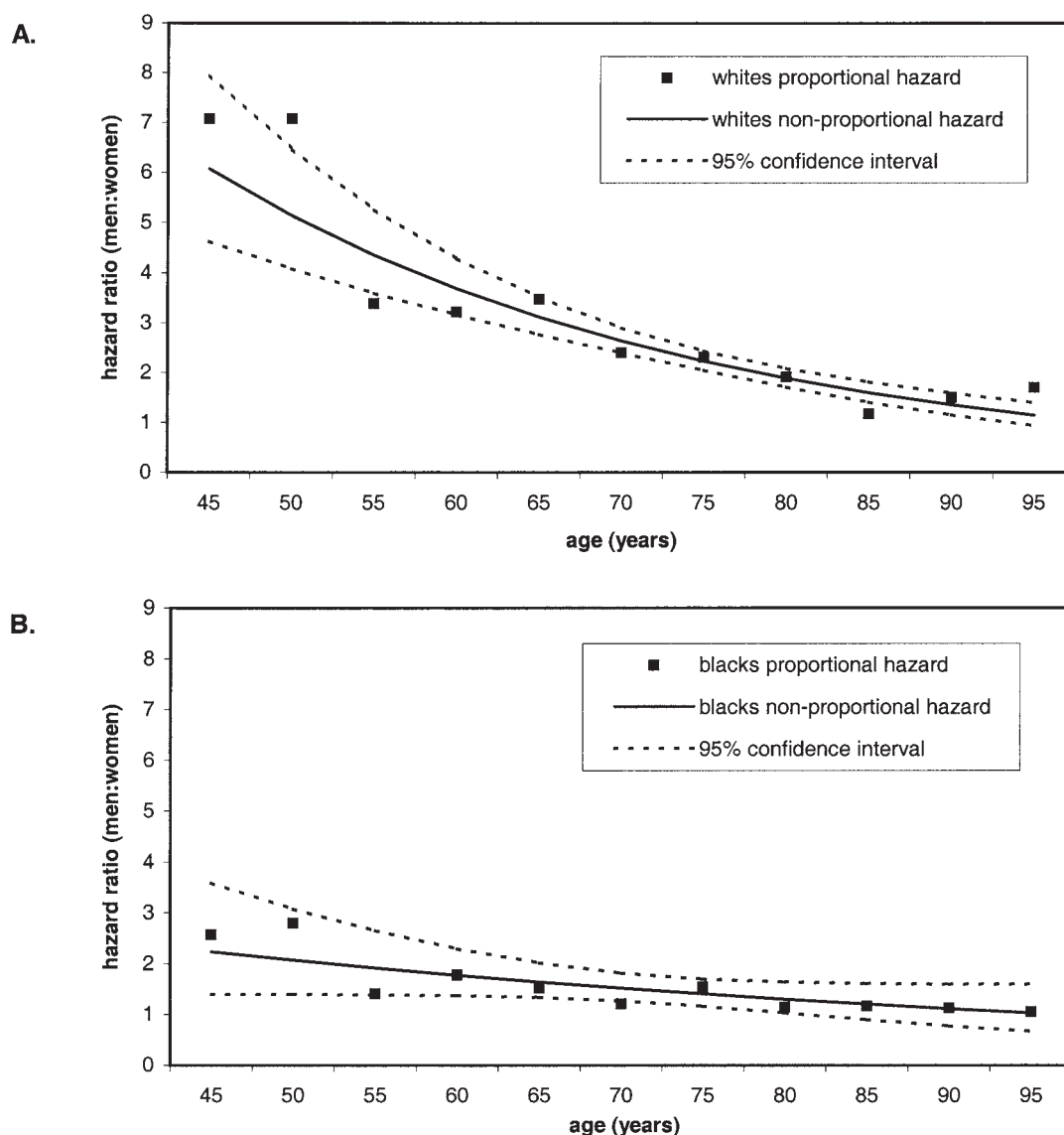


**FIG. 1.** Age-specific CHD mortality rates in men compared with women. The horizontal lines illustrate the lag times of CHD mortality rates between men and women. (A) Whites. The lag time is 10–15 years at younger ages and decreases with age. (B) Blacks. The lag time is 5–10 years.

model are represented by a continuous curve. At age 45, white men were at 6.1 times the risk of white women (CI 4.6–8.0), and by age 95, the CHD mortality risk in men was similar to that in women (HR 1.1, CI 0.9–1.4). In blacks, the male/female CHD mortality HR calculated from the non-proportional model was 2.2 (CI 1.4–3.6) and decreased to 1.0 (CI 0.7–1.6) for the same age groups. For both blacks and whites, the age-specific proportional HRs were similar to the HRs calculated with the nonproportional hazards model.

Unadjusted and adjusted gender HRs for blacks and whites are shown in Figure 3. For

whites, adjustment for risk factors partially attenuated gender differences in the younger age groups, such that men were at 4.8 times the risk of women at age 45 (CI 3.4–6.8) compared with 6.1 times the risk using unadjusted data (CI 5.1–8.6). For blacks, adjustment for risk factors decreased HRs from 2.2-fold to 1.9-fold increased risk in 45-year-old men compared with women (CI 1.4–3.6 unadjusted, 1.1–3.1 adjusted). Despite the partial attenuation of the gender gap in whites in the younger age groups, the decrease in the gender gap with age remained much more pronounced in whites than in blacks.



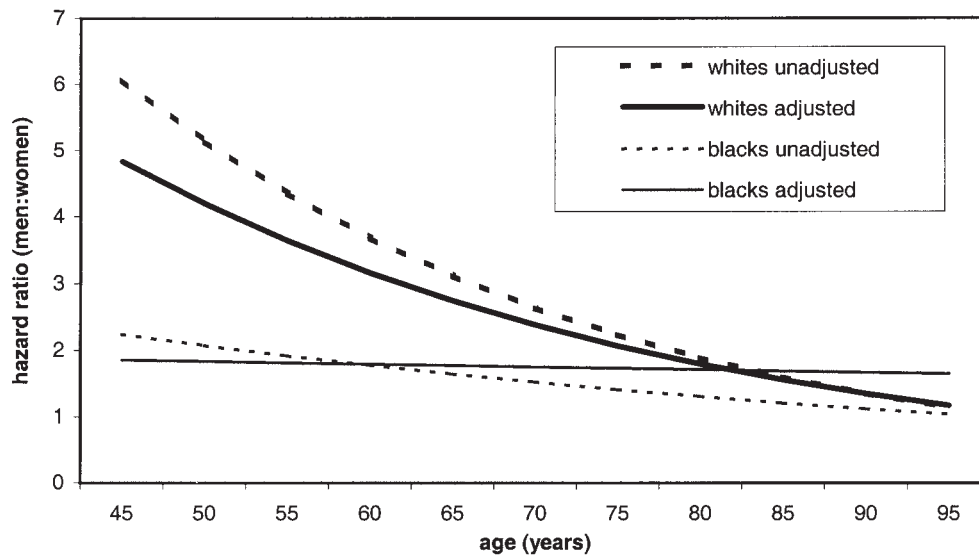
**FIG. 2.** Unadjusted male/female CHD mortality HRs. Age-specific HR calculated from proportional (data points) and nonproportional hazards regression models (continuous line) change with age. **(A)** Whites. The HR decreases significantly with age ( $p < 0.0001$ ). **(B)** Blacks. There is no significant decrease of the gender gap with age ( $p = 0.07$ ).

For both unadjusted and adjusted data in whites, the gender HR decreased significantly with age ( $p < 0.0001$  unadjusted and adjusted) but not in blacks ( $p = 0.07$  unadjusted,  $p = 0.73$  adjusted). The difference between blacks and whites in the age-related trend in the gender gap was highly significant ( $p < 0.0001$  unadjusted and adjusted).

Black/white HRs for same-sex groups are shown in Figure 4. Ethnic differences were most pronounced in women at younger ages. At age 45, black women were at 4.3 times the risk of white women (CI 2.9-6.3). This ethnic difference decreased with age. In men, blacks and whites

were at similar CHD mortality risk in all age groups.

When restricting data to events occurring within 10 years of baseline examinations, the discrepancy between the gender gap in blacks and whites was strikingly similar to previous analyses. Secondary analyses examining a possible time period effect showed that the difference between ethnic groups remained statistically significant when comparing trends by both decades of baseline examination and decades of birth year. The same trend was also observed when each cohort was individually examined and when analyses were restricted to cohorts with  $>10\%$  blacks.



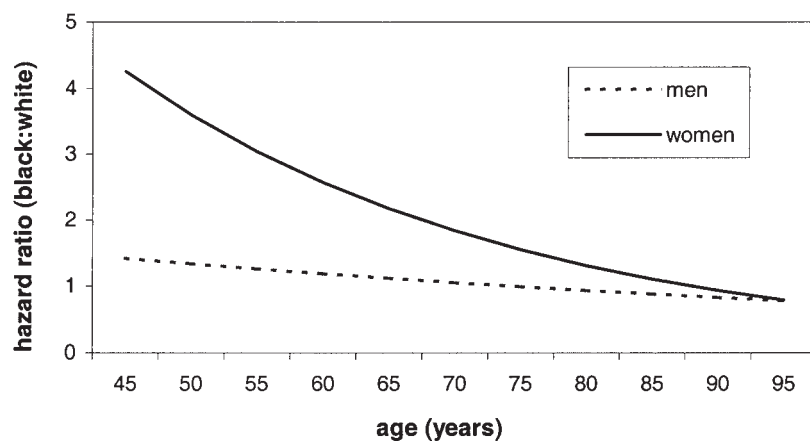
**FIG. 3.** Male/female CHD mortality HRs for whites and blacks, unadjusted and adjusted for risk factors. Adjustment for risk factors partially attenuated the gender gap. However, black/white differences in the age dependency of the gender gap remained ( $p = 0.001$  adjusted). Adjusted risk factors included total cholesterol, diastolic and systolic blood pressures, BMI, smoking, diabetes, education, cohort, blood pressure medication, age.

## DISCUSSION

The main finding of this study was that, in the United States, the gender gap in CHD mortality was more pronounced in whites compared with blacks in the younger age groups. The gender gap in whites narrowed with age, whereas gender differences in blacks did not vary significantly with age. The ethnic difference was primarily due to higher CHD mortality rates in black women compared with white women, in the setting of similar rates in black and white men. We also showed that CHD mortality rates in white women lagged 10–15 years behind those of white men, whereas

in blacks, the lag time between men and women was 5–10 years. The striking differences in the gender gap and lag times between blacks and whites were not explained by adjustment for established risk factors, differential time of follow-up, or secular trends between study periods.

Previous studies examining the relation between age and gender differences in CHD mortality were limited to predominantly white populations. Wingard et al.<sup>5</sup> showed a 10-fold increased risk in men compared with women at ages 50–59, which decreased to a 4.8-fold risk at ages 60–69. Similarly, a Finnish study showed the relative risk (RR) between men and women to de-



**FIG. 4.** Black/white CHD mortality HRs for same-sex groups. At age 45, black women were at 4.3-fold increased risk compared with white women, whereas black men were at 1.4-fold increased risk compared with white men.

cline with age from 9.2 (ages 25–49) to 2.9 (ages 60–64).<sup>15</sup> After adjustment for risk factors in both studies, the age-adjusted RR between men and women decreased from 4.8 to 2.0 and from 5.0 to 3.2, respectively. Both the decrease in gender differences with age and the partial attenuation of the gender gap after risk factor adjustment are consistent with our data in whites.

Our study had the advantage of extended mortality follow-up into older ages, and we were able to show that the narrowing of the gender gap in whites continued into older ages and disappeared completely by age 95. Previous studies of gender differences had limited age ranges because of shorter follow-up times and were also limited by the use of proportional hazards models that assume a constant risk with respect to time. We showed a significant interaction between age and gender in whites. Thus, it was more appropriate to use a nonproportional hazards model in order to examine the age dependency of the gender gap, as it allowed the effect of gender to change with age in a continuous fashion. Instead of stratifying the data into different age groups, this model allowed the incorporation of all data into one model and maximized power.

Several explanations for the gender difference in CHD mortality rates have been proposed. It has been suggested that men and women are affected differently by risk factors. Data from the Renfrew-Paisley Study showed that for a given level of risk factor, the absolute risk of CHD is much lower in women than in men.<sup>34</sup> Thus, adjusting for absolute risk factor levels may not account for a differential impact of a given risk factor.

Estrogen has been suggested to play a cardioprotective role in women and could contribute to gender differences. For example, data from Framingham showed a 4-fold increased CHD incidence rate in premenopausal compared with postmenopausal women of the same ages.<sup>4</sup> However, the administration of exogenous estrogen has not shown any beneficial effect from a cardiovascular standpoint in men or women.<sup>18,35</sup> The role of endogenous estrogen in the gender gap is unclear, and the gender gap discrepancy between whites and blacks in our study suggests that estrogen may not be the only factor influencing gender differences. This is also supported by dramatic variations of the gender gap in CHD mortality across time periods and geography.<sup>36</sup>

Internationally, CHD mortality rates have been

shown to be consistently higher in men compared with women,<sup>37</sup> although data from the World Health Organization (WHO) showed tremendous variation in gender differences with age, secular trend, and individual country.<sup>36</sup> Male/female CHD mortality ratios ranged from as low as 1.4 (China, Cuba) to as high as 2.9 (Poland), suggesting that the gender gap may be a phenomenon of predominantly industrialized countries and that socioeconomic status (SES) may play a role in gender variation. Although no specific data on SES was analyzed in our study, educational status as a proxy of SES has been shown to vary by ethnic group and is predictive of CHD mortality.<sup>9,12,38,39</sup> Adjustment for educational status partially attenuated the gender gap but did not fully explain gender or ethnic differences.

Black/white HRs within same-sex groups indicate that the gender gap discrepancy between blacks and whites in our study was primarily due to higher mortality rates in black women compared with white women. This is consistent with previous data describing black and white differences in CHD mortality in same-sex groups.<sup>8,9,11,40</sup> Gillum<sup>13</sup> noted that black women were at 1.5 times the risk of white women for dying of heart disease, whereas black and white men were at equal risk, and that black/white differences were more pronounced at younger ages.

In contrast, investigators of the Charleston Heart Study compared black/white ratios in same-sex groups and found no significant ethnic differences in CHD mortality rates after adjustment for risk factors, although there were significant gender differences within the same ethnicity.<sup>41</sup> These results may differ from ours because the use of a Cox proportional hazards regression model did not account for the age dependency in gender/ethnic differences. When reanalyzing the data from the Charleston Heart Study included in our analysis using the nonproportional model, we found significant gender/ethnic differences in the younger age groups.

The elevated CHD risk in black women compared with white women in the setting of a similar risk in black men compared with white men suggests that genetic background, SES, and emerging risk factors may contribute to gender differences. It is plausible that access to health-care and preventive care and patient compliance could account for black and white differences, although these measures were beyond the scope of our analysis. Although black women generally

have favorable lipoprotein profiles compared with white women, as was seen in the lower total cholesterol levels in our study, they have higher lipoprotein(a) and homocysteine levels than white women, which may contribute to the increased cardiovascular risk in black women.<sup>42</sup> In this population, black women were both more obese and had a greater prevalence of diabetes than the other three groups. The constellation of risk factors in the metabolic syndrome were also incompletely adjusted for, including insulin resistance and prothrombotic states. Our study was limited in the ability to adjust for such emerging risk factors, as well as diet and exercise patterns, which could have contributed to ethnic differences in the gender gap.

Another limitation of this study is the combination of data from several different cohorts with varying methods of data collection. To examine the robustness of data between studies, several analytical techniques were used, such as ranking continuous variables by quintiles within each cohort, and data were found to be highly consistent between cohorts. In addition, cohort-specific analyses were consistent with our pooled analysis despite limited power.

Variation in time from baseline measurement to event could have caused misclassification of risk in older ages, as the incidence of nonfatal CHD was not monitored. However, when limiting the analysis to events occurring within 10 years of study entry, trends were not materially different.

Another potential limitation is the misclassification of ICD codes. A greater proportion of CHD deaths have been noted to occur outside of the hospital in blacks than whites, leading to less accurate coding.<sup>43</sup> Nevertheless, both black men and black women would presumably be influenced similarly by miscoding, and risk ratios between genders would still be representative.

Finally, our analysis examined CHD mortality, and the ethnic differences in the gender gap noted here might be different from those for nonfatal CHD.

## CONCLUSIONS

We showed a significant difference in the gender gap in CHD mortality between blacks and whites. In whites, gender differences were most pronounced in the younger age groups, where men were at 6-fold increased risk compared with wo-

men. In comparison, gender differences in blacks were less striking, and black men were at 2-fold increased risk compared with women at younger ages. In both blacks and whites, CHD mortality risk was similar between men and women in the older age groups. The black/white discrepancy in the gender gap was also seen in comparing absolute mortality rates. The lag time between mortality rates in white men and women was 10–15 years at younger ages and shortened with age, whereas the lag time in blacks remained 5–10 years at all ages. When adjusted for risk factors, time period, cohort effect, and differential follow-up time, these black/white differences remained, suggesting the reason for the observed discrepancy is complex.

The black/white difference in the gender gap suggests that estrogen may not be the only factor contributing to gender differences. These data may be important in providing insight into the complex relation among age, race, and gender as determinants of CHD mortality. Future research should consider social, environmental, and other modifiable factors that may contribute to gender and ethnic differences in CVD. An understanding of the increased CHD risk observed particularly in black compared with white women may be of importance in considering future prevention strategies.

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