AMERICAN JOURNAL OF EPIDEMIOLOGY
Vol. 131, No. 3
Printed in U.S.A.

SEX DIFFERENCES IN TIME FROM SELF-REPORTED HEART TROUBLE TO HEART DISEASE DEATH IN THE ALAMEDA COUNTY STUDY

SIGNIFICANCE OF TIME DEPENDENCE OF RISK VARIABLE EFFECTS

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Cohn, B. A. (California Public Health Foundation, Berkeley, CA 94704), D. L. Wingard, R. D. Cohen, P. M. Cirillo, and G. A. Kaplan. Sex differences in time from self-reported heart trouble to heart disease death in the Alameda County Study: significance of time dependence of risk variable effects. *Am J Epidemiol* 1990;131:434–42.

In a previous analysis from the Alameda County Study, it was observed that although men had higher heart disease mortality rates than women, there was no male excess in the prevalence of self-reported heart disease morbidity at baseline or in new reports of morbidity 9 years past baseline. This apparent contradiction might occur because women report less severe heart disease than men. In the present study, this hypothesis was evaluated by examining whether self-reported heart trouble was more strongly associated with subsequent heart disease mortality for men than for women in a representative sample of the population of Alameda County, California, selected in 1965 and followed for mortality for 19 years (n = 3,742). In a time-dependent Cox model, self-reported heart trouble was a stronger predictor of heart disease mortality for men, but only during the early years of follow-up (p = 0.00). This effect was due to a shorter time to death for men who reported heart trouble. The relative hazard for men reporting heart trouble was 6.6 (95% confidence interval (CI) 3.7–11.6) at baseline, declining to 3.2 (95% CI 2.2–4.5) by 5 years past baseline and 1.5 (95% CI 0.9–2.5) by 10 years past baseline. Self-reported heart trouble was a consistent predictor of subsequent heart disease mortality for women over the 19-year follow-up period (relative hazard = 2.0, 95% CI 1.4–2.8). Sex differences in the prognosis of self-reported heart trouble were masked in non-time-dependent analyses. These results illustrate that consideration of time dependence may be required for meaningful analysis of long-term cohort studies. Possible explanations of the shorter time to death for men who reported heart trouble are discussed.

coronary disease; morbidity; mortality, prospective studies; sex factors; survival; time factors

Data from long-term cohort studies are often used to test hypotheses that were not the primary focus of the original investigation. Such secondary analyses present

Received for publication April 17, 1989, and in final form September 5, 1989.

Abbreviation: CI, confidence interval.

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certain dilemmas for the investigator. One of these is whether to use the entire follow-up period or only a part of it. Statistical power considerations suggest using the entire period available for rare outcomes, in order to maximize the number of observable outcomes. However, if the relations under investigation vary with the length of follow-up (time dependence), it may be better to examine one or more subsets of the follow-up period instead of its entirety. In this paper, the importance and feasibility of considering time dependence in secondary analysis is illustrated with an example from the study of sex differences in associations between self-reported heart trouble and subsequent heart disease mortality in the Alameda County cohort, a representative sample of the population of Alameda County, California.

In previous reports, it has been observed that although women live longer than men in developed countries (1–4), they report more morbidity (1, 3, 5). In the first prospective analysis of sex differences in morbidity and mortality within one population-based cohort (the Alameda County Study), women were as likely or more likely to report new heart disease morbidity, but men had higher heart disease mortality rates (6). This apparent contradiction might have occurred because women reported less severe heart disease than men. To test this hypothesis, in the present study we compared the strength of the association between self-reported heart disease morbidity and subsequent ischemic heart disease mortality for men versus women over time. Specifically, we hypothesized that time to death would be shorter for men if their disease was more severe. This would result in sex differences in the time dependence of the association between self-reported heart trouble and subsequent heart disease mortality.

While techniques for assessing time dependence have been available for some time (7, 8), consideration of time dependence for addressing specific research questions in secondary analysis of epidemiologic data has not been frequently used. This paper demonstrates the utility of simple graphic methods for identifying the time dependence of associations, using an example from the Alameda County Study.

Materials and methods

Study population

The study sample consisted of adults living in Alameda County, California, who participated in a 1965 survey of physical, social, and psychologic indicators of health conducted by the Human Population Laboratory of the California Department of Health Services. The cohort was 81 percent white, 12 percent black, and 7 percent other races. The sampling procedure, explained in greater detail elsewhere (9), elicited an 86 percent response rate to a mailed questionnaire. The male and female response rates were virtually equal (85 percent and 87 percent, respectively). When compared with respondents, the small group of nonrespondents included slightly more older people, whites, and retired, single, and widowed persons. However, the differences between respondents and nonrespondents have a negligible effect on population estimates, and these respondents have been judged to be a representative sample of adults living in Alameda County, California, in 1965 (10). The present analyses include 2,046 women and 1,696 men who were either white or black, were aged 40 years or more at baseline, and had responded to the following question concerning the presence of "heart trouble" in the preceding 12 months: "Here is a list of medical conditions that usually last for some time. Have you had any of these conditions during the past 12 months?" (Heart trouble was listed with a yes or no response

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This research was supported by National Institute of Aging Grants R01-AG05687 and R29-AG08387.

The authors thank Gerald N. De Lorenze for his assistance with data analysis.

possible.) Younger persons were excluded because of low heart disease mortality, and other races were excluded because of possible language and cultural differences in the self-report of heart trouble. Among men and women in these age and race categories, only six women and three men did not answer the heart trouble question.

Data from the heart trouble question which are used in the present analysis have been used in previous reports from the Alameda County Study (11–13). In these previous analyses, self-reported heart trouble demonstrated predictive validity. The prevalence of self-reported heart trouble in a 1974 population sample of Alameda County as estimated by this same questionnaire item was very similar to that reported for a national sample by the Health Interview Survey, conducted in 1972 (13).

Mortality ascertainment

Mortality data were collected from 1965 through 1983. Mortality was ascertained using a computer-matching linkage with the California Death Registry to obtain the death certificates of persons who had died in California or had died outside the state with notification to California. The linkage process is described in detail elsewhere (14, 15). Loss to follow-up was estimated from a 1974 follow-up of the 1965 cohort and was approximately 4 percent over 9 years.

Underlying causes of death were coded according to the Eighth Revision of the *International Classification of Diseases, Adapted.* For the purposes of these analyses, ischemic heart disease deaths were defined by codes 410–414. There were 204 ischemic heart disease deaths among women and 242 ischemic heart disease deaths among men during the 19-year follow-up period for this sample.

Analysis

The initial hypothesis to be tested was whether the report of heart trouble was a stronger predictor of subsequent ischemic heart disease mortality for men than for women. In statistical terms, this hypothesis is an interaction hypothesis. The statistical question was: Is there an interaction between sex and the report of heart trouble for predicting ischemic heart disease mortality? The Cox proportional hazards model for a 19-year follow-up period was initially used to address this question. The variables in the model were age, sex, report of heart trouble, and a product term, sex × heart trouble, which represented the hypothesized interaction. The results of this initial analysis suggested no interaction between sex and report of heart trouble, prompting further analyses described below.

Sex differences in the time dependence of the heart trouble associations were then examined. It was hypothesized that the effect of heart trouble would be greater for men than for women early in the follow-up period if men were reporting more severe heart trouble than women. That is, an interaction between heart trouble and sex might occur early but not later in the follow-up period; otherwise stated, the interaction would be time dependent. In terms of the Cox model, this would mean that the ratio of the relative hazard for men reporting heart trouble to that for women reporting heart trouble would vary over time. Such an effect could occur if, for example, the heart trouble relative hazard was constant over time for one sex but not for the other.

To examine sex differences in the time dependence of the heart trouble relative hazard, we stratified the data by sex and the presence or absence of heart trouble. Within each of the four strata, the survival function was estimated by fitting a Cox model adjusted for age. To facilitate the comparison of heart trouble relative hazards over time for men and women, a transformation of the estimated survival curves, −log (−log survival), was plotted against years of follow-up by heart trouble status for each sex.

The distance between the transformed curves for those with heart trouble and those without heart trouble provides an

estimate of the log of the heart trouble relative hazard (8). A constant distance, i.e., parallel curves, over the length of follow-up implies that the relative hazard is not varying over time. Changing distances between curves over the follow-up period suggest time dependence of the relative hazard. These pairs of curves were examined sex-specifically to compare the time dependence of the heart trouble relative hazards for men and women.

We emphasize that the constancy (or the absence of constancy) of the relative hazard over time which is revealed by the parallelism (or the lack of parallelism) of the transformed survival curves cannot be easily assessed by looking at the original untransformed survival curves. In fact, examination of the transformed curves is widely recommended as a means of checking the proportional hazard assumption (constancy of the relative hazard over time) which underlies the Cox model (8, 16, 17).

Three other approaches were also used in this study to examine sex differences in the time dependence of the heart trouble relative hazard. First, Cox proportional hazards models containing age, sex, report of heart trouble, and the product term, sex × report of heart trouble, were fitted using different lengths of follow-up. These analyses illustrated how the result obtained differed with the length of follow-up. In these analyses, the coefficient of the product term provided an estimate of the strength of the interaction between sex and the report of heart trouble.

Second, the cumulative percent distribution of ischemic heart disease deaths over time was examined by sex and heart trouble status to illustrate sex differences in time to death for those who did and did not report heart trouble at baseline.

Third, a time-dependent Cox proportional hazards model (7) was fitted to the data containing the following terms: age, sex, report of heart trouble, sex × report of heart trouble, and sex × report of heart trouble × time, where time is years since the beginning of follow-up. The estimated three-way interaction between report of heart trouble, sex, and time is a means of quantifying time dependence of the interaction between sex and self-reported heart trouble, evidenced graphically by transformed survival curves. A significant coefficient for the sex × report of heart trouble × time term implies that the association between heart trouble and mortality varies with time for men. Lack of significance for this coefficient implies no time dependence of the association for men. The model was fitted using the BMDP program 2L for survival analysis with covariates (18).

RESULTS

Table 1 presents sex-specific ischemic heart disease mortality rates by the presence or absence of self-reported heart trouble for the study sample. Self-reported heart trouble was associated with greater heart disease mortality for both men and women. The relative hazard for those reporting heart trouble was 2.9 for men and 3.6 for women. However, this apparent sex difference was not statistically significant.

Figure 1 presents age-adjusted −log (−log survival) curves for ischemic heart disease mortality for men and women with heart trouble and without heart trouble. For women, the curves for those with and those without heart trouble were essentially parallel, indicating that the heart trouble relative hazard remained constant over time.

TABLE 1

Ischemic heart disease mortality, by sex and the presence or absence of self-reported heart trouble, Alameda County Study, 1965–1983

	No. of deaths	Risk (%)
Males		
Heart trouble	42	36.2
No heart trouble	200	12.7
Females		
Heart trouble	43	30.5
No heart trouble	161	8.5

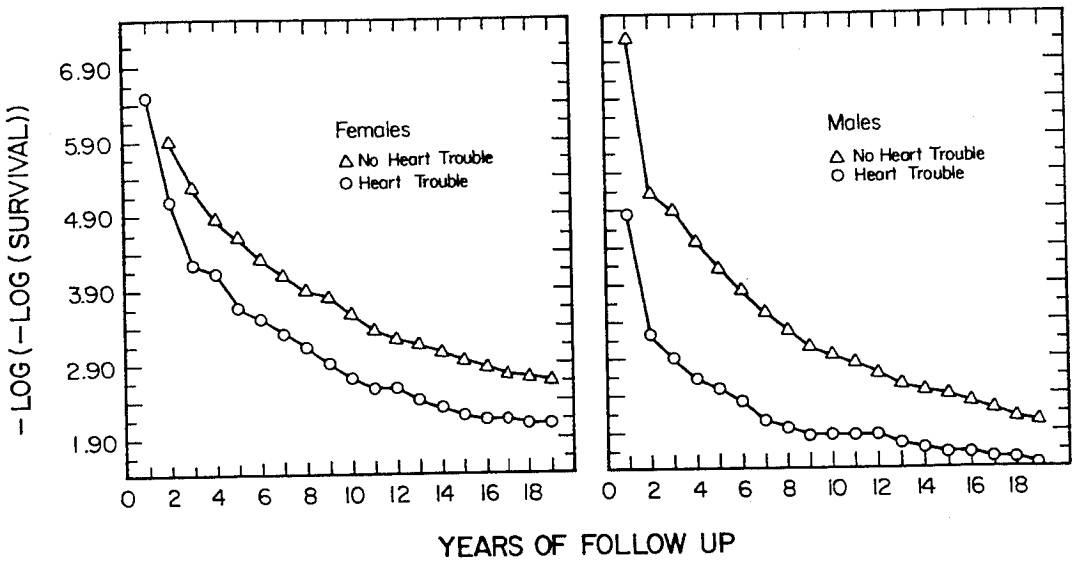

FIGURE 1. Age-adjusted, sex-specific −log (−log survival) curves for ischemic heart disease, by the presence or absence of self-reported heart trouble, Alameda County Study, 1965–1983.

For men, the curves for those with and those without heart trouble were not parallel, indicating a large heart trouble relative hazard early in the follow-up period which declined as length of follow-up increased. Thus, these curves indicate time dependence of the heart trouble relative hazard only for men.

The sex difference in the time dependence of the heart trouble relative hazard resulted in an interaction between heart trouble and sex during the early follow-up period which declined as follow-up increased. This effect is illustrated in figure 2, which presents age-adjusted, sex-specific associations between self-reported heart trouble and ischemic heart disease mortality, estimated by Cox models containing age, sex, heart trouble, and sex × heart trouble for different lengths of follow-up. The sex difference in the heart trouble relative hazard declined as the length of follow-up increased. The report of heart trouble was a substantially stronger predictor of ischemic heart disease mortality for men during the early follow-up period only.

The shorter time to ischemic heart disease death for men who reported heart trouble is illustrated in figure 3. Fifty percent

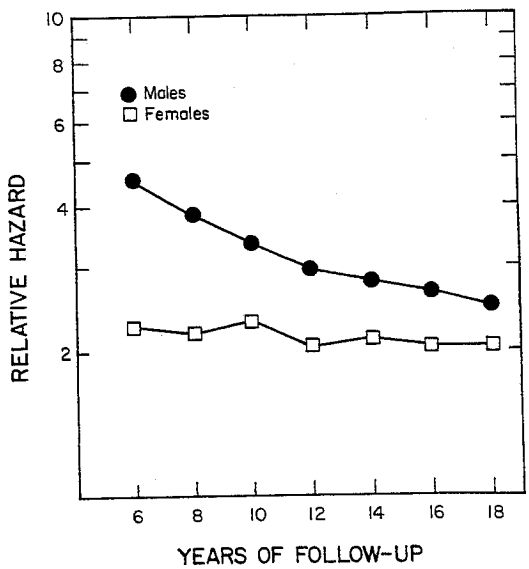

FIGURE 2. Age-adjusted, sex-specific associations between self-reported heart trouble and ischemic heart disease mortality, by years of follow-up, Alameda County Study, 1965–1983. Relative hazards (heart trouble present/absent) were estimated by non-time-dependent Cox models. Each point is estimated by a Cox model containing age, sex, self-reported heart trouble, and sex × self-reported heart trouble for the length of follow-up indicated.

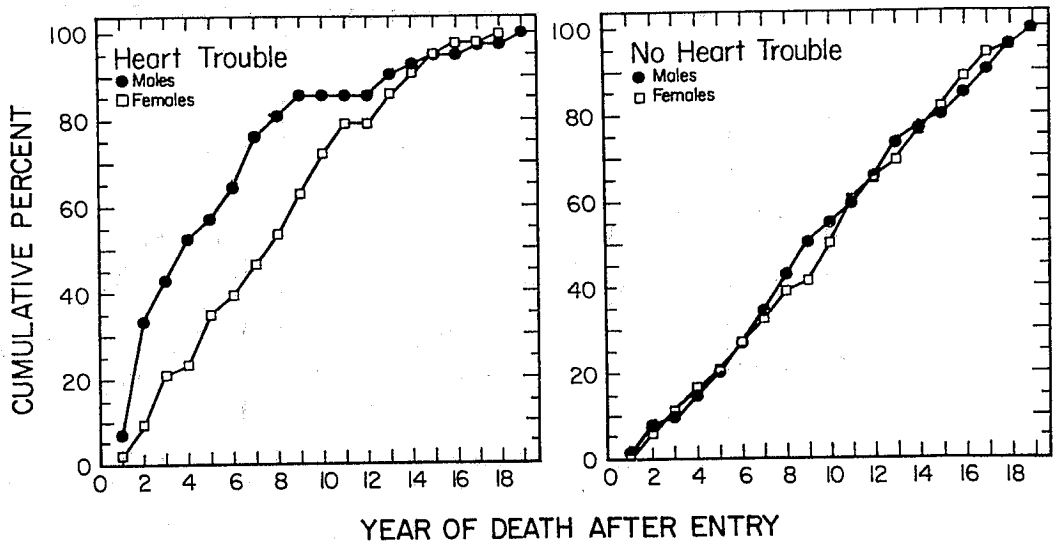

FIGURE 3. Cumulative percent distribution of ischemic heart disease deaths, by sex and the presence or absence of self-reported heart trouble, Alameda County Study, 1965–1983.

of the ischemic heart disease deaths among men who reported heart trouble occurred within 3 years of follow-up, compared with 7 years for women who reported heart trouble. In contrast, the cumulative percent distribution of ischemic heart disease deaths over time among those not reporting heart trouble was virtually the same for men and women. Sex differences in the age distribution of individuals who reported heart trouble probably do not explain the earlier mortality seen in figure 3 among males who reported heart trouble. Although men who reported heart trouble were younger (27.5 percent were aged 40–55 years, compared with 17.0 percent for women), only five male deaths and two female deaths occurred in the 40–55 age group. Consequently, the cumulative percent distribution of heart disease deaths for individuals over age 55 who reported heart trouble is practically identical to the curve for all ages shown in figure 3.

In the time-dependent Cox model, the relative hazard for ischemic heart disease mortality among men reporting heart trouble was estimated as a decreasing function of time given by $\exp(1.88 - 0.14t)$, where t is years of follow-up. The coefficient of t in this expression corresponds to the regression coefficient for the heart trouble × sex × time interaction term and was statistically significant ($p = 0.00$). These results suggest that the effect of self-reported heart trouble declined over time for men. As figures 1 and 3 show, this decline can be explained by a short time to death for men who reported heart trouble. There was no indication of an acceleration of ischemic heart disease mortality over time among men who did not report heart trouble.

At baseline, the estimated relative hazard for men reporting heart trouble was 6.6 (95 percent confidence interval (CI) 3.7–11.6), declining to 4.9 (95 percent CI 3.1 –7.7) by 2 years past baseline, 3.2 (95 percent CI 2.2–4.5) by 5 years past baseline, and 1.5 (95 percent CI 0.9–2.5) by 10 years past baseline. The corresponding heart trouble relative hazard for women during the entire follow-up period, estimated by the same Cox model, was 2.0 (95 percent CI 1.4–2.8). There was no evidence of time dependence for the heart trouble relative hazard for women. These results suggest that self-reported heart trouble was a stronger predictor of subsequent ischemic heart disease mortality for men early in the follow-up period, but this sex difference diminished with time. Thus, a sex difference in the

association between self-reported heart trouble and subsequent ischemic heart disease mortality could not be observed in analyses which did not evaluate the hypothesis of sex differences in the time dependence of this association.

Discussion

This study demonstrates that the length of follow-up is an important factor to consider in secondary analysis of cohort studies. Because of the time dependence of the sex-heart trouble interaction illustrated in these data, either a Cox or a logistic analysis for a 19-year follow-up period would have resulted in rejection of the hypothesis that report of heart trouble is a stronger predictor of subsequent ischemic heart disease mortality for men. By evaluating the hypothesis of time dependence of this interaction, we observed a stronger association between self-reported heart trouble and ischemic heart disease mortality for men during the early years of follow-up.

In this study, self-reported heart trouble predicted subsequent heart disease mortality for women consistently over the entire 19-year period, but was associated with a shorter time to death for men. This finding suggests that women's report of heart trouble is valid but is associated with a longer survival. In addition, this finding is logically consistent with the earlier observation of a male excess in mortality and a female excess in new morbidity for heart disease in the Alameda County Study over a 9-year follow-up period (6). It is also consistent with a recent report from the Framingham Study which found a strong survival advantage for women subsequent to myocardial infarction (19). There are several possible explanations for these findings.

First, sex differences in the perception of illness might lead women to report heart disease at an earlier, less severe stage. Although this hypothesis is often discussed as an explanation for excess morbidity reported by women, there is little empiric evidence to support it (3, 20). Women do report more symptoms and illness than men (5, 21–24). However, experimental studies of the accuracy of symptom reporting do not indicate sex differences (22). There is conflicting evidence regarding sex differences in the validity of illness and symptom reporting when measured against medical records (20, 24 [see references 25–31 as reviewed by Waldron (24)]). Sex differences in this validity measure depend upon the type of morbidity considered, and the question of whether men or women make more valid illness reports as measured by this criterion remains unresolved (24). The lack of sex differences in the incidence of silent myocardial infarction (24, 32) and a lack of sex differences in the interval between onset of myocardial infarction symptoms and initiation of medical care (24) suggest no sex differences in sensitivity to this manifestation of heart disease.

Sex differences in risk behaviors could explain the shorter time to death for men who reported heart trouble. Although behavioral factors have been shown to contribute to sex differences in mortality (1, 4, 33), some high-risk behaviors are more prevalent in women (e.g., physical inactivity), while others are more prevalent in men (e.g., smoking) (33). Overall, sex differences in behavioral factors did not explain the male excess in all-cause or ischemic heart disease mortality observed in the Alameda County cohort, the Rancho Bernardo cohort, or a sample of the San Francisco-Oakland Kaiser Permanente population (all reviewed in reference 34). However, it is possible that behavioral factors could explain the sex differences in time to death observed in the present study for those who reported heart trouble. A test of this hypothesis is in progress in the Alameda County cohort.

Earlier, more frequent, or more compliant use of medical care could also explain the longer time to death for women who reported heart trouble. Previous studies suggest that women are more likely to have a regular physician (1, 3, 23), visit physicians (5), take more time off from work or

housework in response to illness (3, 35), and use outpatient services (36). There are conflicting reports as to whether women are more likely to seek a physician's advice for chronic conditions (17, 37), and there is little evidence that men are more likely to delay seeking care for a serious illness (3, 24). The role of preventive care use, having a regular physician, and frequency of physician visits in explaining the sex difference in time to death among those reporting heart trouble is currently being examined in the Alameda County Study cohort.

In addition, sex differences in the disease process which result in a longer time to death from the first perception of symptoms for women could explain the findings of the present study. Sex differences in atherosclerosis at angiography (38), in the distribution of ischemic heart disease manifestations (39), and in survival subsequent to myocardial infarction (19) support the hypothesis that there are sex differences in the natural history of ischemic heart disease (24). The incidence of sudden death and myocardial infarction is higher for men (39, 40), while sex ratios for angina pectoris depend upon age and length of follow-up such that the male excess is less and is not consistently observed (40, 41). Even though women live longer than men, heart disease is the leading cause of death in both sexes in the United States (1). These observations and the findings of the present study are consistent with the hypothesis that women have longer survival after self-report of heart disease.

In summary, this study has demonstrated the utility and feasibility of examining time dependence of risk factor effects in the secondary analysis of cohort studies. Findings from this study are consistent with the hypothesis that self-reported heart trouble has different prognostic implications for men and women, although predictive validity was demonstrated for both men and women. Findings have suggested testable hypotheses which may help unravel the apparent contradiction between the female excess in morbidity and the male excess in mortality reported in these data for heart disease and noted more generally in the literature on sex differences in health. Further tests of these hypotheses are under way in the Alameda County Study.

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