Sex differential in the relationship of electrocardiographic ST-T abnormalities to risk of coronary death: 11.5 year follow-up findings of the Chicago Heart Association Detection Project in Industry

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ABSTRACT The independent contributions of ST segment depression and/or T wave abnormality (ST-T abnormalities) on the baseline resting electrocardiogram to risk of 11.5 year coronary heart disease (CHD) mortality were explored among 9203 white men and 7818 white women who were 40 to 64 years old and without definite CHD at entry in the Chicago Heart Association Detection Project in Industry. At baseline, prevalence rates of ST-T abnormalities were age related for both sexes, and at every age the rate was higher in women than men (age-adjusted prevalence rates 12.3% and 8.1%, respectively). Univariate analysis showed that ST-T abnormalities were associated with significantly increased risk of death from CHD for both men and women. However, men with ST-T abnormalities had much greater age-adjusted and multiple risk factor–adjusted absolute excess risk and relative risk than women with such electrocardiographic abnormalities. When baseline age, diastolic pressure, serum cholesterol, cigarettes/day, history of diabetes, and baseline use of antihypertensive medication were included in the multivariate analysis, ST-T abnormalities remained significantly related to death from CHD in men but not women. The interaction term between sex and ST-T abnormalities was at a borderline level of statistical significance by Cox regression analysis. In conclusion, ST-T abnormalities indicate an increased risk of subsequent death from CHD independent of major coronary risk factors for middle-aged U.S. men, but this is not clearly so for women.


ST SEGMENT DEPRESSION and/or T wave abnormalities on the resting electrocardiogram are among the most common findings encountered in clinical examination of patients, in screening asymptomatic adults, and in epidemiologic surveys. The association of ST-T abnormalities with increased coronary heart disease (CHD) mortality was reported in insurance experience over 30 years ago.1, 2 Subsequently, the adverse prognosis of such individuals with electrocardiographic (ECG) abnormalities was noted by others.3–10 However, almost all studies combined men and women in one observation group,1–3, 7 or dealt with men only.4, 6, 8–10 Also, most studies did not examine whether the relationship of these ECG abnormalities to mortality was independent of other traits, including age and the established coronary risk factors. The purpose of this study was to assess whether there is an independent relationship of ST-T abnormalities to risk of CHD mortality in men and women, and whether there is a sex differential in this regard.

Materials and methods

Study population. The Chicago Heart Association Detection Project in Industry is a cross-sectional and prospective study of 39,573 young adult and middle-aged men and women, most of them white or black. The baseline survey was done from late 1967 through early 1973 in 84 cooperating companies and organizations in the Chicago area.11–13 Subjects for this study
were selected from a cohort of 18,218 white men and women age 40 to 64 years at baseline. The study excluded 88 persons who had evidence of definite myocardial infarction on their baseline electrocardiograms. Since the focus of this study was on the prognostic significance of primary ST-T abnormalities, 389 other persons were excluded because they had one or more of the following ECG abnormalities, since they could be associated with secondary ST-T change and/or affect prognosis: ST segment elevation (five persons), right or left ventricular hypertrophy (90 persons), complete bundle branch block or intraventricular block (267 persons), complete or second-degree atrioventricular block (three persons), ventricular rhythm (one person), atrial fibrillation or flutter (35 persons), Wolff-Parkinson-White syndrome (four persons). In addition to these exclusions, 332 individuals were lost to follow-up and complete baseline data on all relevant variables were lacking for 388, who were also excluded. The population therefore consisted of 17,021 persons, 9203 men and 7818 women.

**ECG and other baseline date.** Over the years of screening, procedures for recording and analyzing the resting electrocardiogram varied as follows: (1) use of six standard limb leads, (2) standard 12-lead electrocardiogram, (3) use for primary ECG screening of the Electro-Cardio-Analyzer Model 400 (ECA), which received signals from leads I, II, aVF, V1, and V5, plus a standard 12-lead electrocardiogram when ECA signals were outside normal limits, (4) use of the ECA to screen, and when it indicated ECG signals within normal limits, a five-lead electrocardiogram (I, II, aVF, V1, and V5) with a standard 12-lead recording when the ECA reading was outside normal limits, (5) ECA and five-lead recordings. The ECA was found to have high sensitivity (92%) for detecting abnormal electrocardiogram.14 When ECA signals were abnormal, a regular electrocardiogram was recorded and the final assessment was based on the latter tracings. All electrocardiograms were read by one cardiologist (J. A. S.), using criteria and forms of the 1960–1962 National Health Examination Survey (NHES), U.S. Public Health Service.15

Criteria for ST segment depression were any of the following (in any of leads I, II, aVL, aVF, and V1 to V6):

1. ST junction depression 1 mm or more.
2. ST-J depression 0.5 to 0.9 mm and ST segment horizontal or downward.
3. No ST-J depression as large as 0.5 mm but downward-sloping ST segment reaching 0.5 mm or more below baseline (T-P interval was baseline).

Criteria for T wave abnormality were any of the following:

1. T wave inversion of 5 mm or more and QRS mainly upright in any one or more of leads I, II, III, aVL, aVF, and V2 to V5.
2. T wave inversion between −1 to −5 mm in any of leads I, II, aVL, and V2 to V5 when R wave was 5 mm or more in aVL or when QRS was mainly upright in aVF.
3. Flat or low-voltage diphasic (±1 mm) T wave with QRS mainly upright in any one or more of leads I, II, and V4 to V6 or when the R wave was 5 mm or more in either aVL or aVF.

In 44% of persons with ST segment depression and 54% of those with T wave abnormality, the two types of abnormality coexisted. The frequent association of ST segment and T wave abnormality, plus clinical thinking that considers them together, led to their combination into one group of primary ST-T abnormalities.

Other baseline data, including blood pressure and serum cholesterol, were obtained in a standardized way based on a single protocol. Data on cigarette smoking, history of physician-diagnosed diabetes, and current use of antihypertensive medication were obtained with a precoded self-administered questionnaire.

**Long-term follow-up of vital status.** Vital status of each participant was ascertained every 5 years after the baseline examination. To date, almost every participant has undergone two or three rounds of follow-up searches. Mean duration of follow-up of the cohort was 11.5 years for both men and women, varying from 0.1 years for early decedents to 19 years. Cause of death was classified from death certificates, without knowledge of baseline findings; the eighth revision of the ICD (International Classification of Diseases, Adapted) was used, with codes 410–414 for CHD.16

**Statistical methods.** Comparison of crude prevalence rates of ST-T abnormalities for the two sexes was by chi-square analysis. The direct method was used to adjust for age (5 year intervals) and for the five different ECG procedures used. The relationship between ST-T abnormalities and CHD mortality was examined by sex in both univariate and multivariate analyses. Age-adjusted cumulative mortality for CHD was calculated by the life table method.17 Age adjustment and multiple CHD risk factor adjustment of mortality was based on a linear model. All adjustments were standardized on a common overall population of two sexes. The multivariate Cox regression model18 was used to examine whether ST-T abnormalities constituted an independent risk factor for death from CHD in men and women. In multivariate analyses, adjustment was made for age, diastolic pressure, serum cholesterol, cigarettes smoked per day, and diabetes. For the 1218 persons on antihypertensive medication, because baseline blood pressure measurements may not have represented their true blood pressure levels, adjustment also was made for the baseline use of antihypertensive medication. Cox regression coefficients with and without control for the five different ECG recording procedures were fit separately for each sex. Since none of the differences for the log-likelihoods between the two models with and without control for the different recording procedures were statistically significant, the results presented are the overall combined data irrespective of the five ECG recording procedures.

**Results**

**Baseline risk factor data for men and women with and without ST-T abnormalities.** Table 1 presents data on baseline age and levels of several major CHD risk factors. For both men and women, persons with ST-T abnormalities compared with those free of these abnormalities were on the average older, with higher systolic and diastolic pressures, higher serum cholesterol, higher prevalence rates of smoking, and more diabetics. These differences were all statistically significant (p < .05) except those for percent smokers among women and number of cigarettes smoked per day and percent with diabetes in both sexes.

**Sex differential in prevalence of ST-T abnormalities.** Data on age-specific prevalence rates of ST-T abnormalities by sex are shown in table 2. Rates were higher with age in both men and women. They were significantly higher in women than in men at every age and for the total cohort. Age-adjusted prevalence rates were 12.3% and 8.1% for women and men, respectively (p < .001). Prevalence rates of ST-T abnormalities were significantly higher for women than men with each of the five ECG recording procedures. After adjustment for ECG procedure, the sex difference
remained significant (12.6\% vs 8.0\%, respectively, \(p < .001\)).

**Relationship by sex of baseline ST-T abnormalities to 11.5 year risk of death from CHD.** Figure 1 compares the age-adjusted cumulative mortality for CHD by sex for persons with and without ST-T abnormalities at baseline. Individuals of both sexes with abnormalities had greater CHD mortality, but this finding was much more prominent in men than women. For women, at each 1 year interval beyond baseline, the age-adjusted cumulative mortality was approximately twice as high for those with ST-T abnormalities as for those without.

**TABLE 2**
Prevalence rates of ST-T abnormalities by age and sex in white men and women 40 to 64 years old at entry to the Chicago Heart Association Detection Project in Industry

<table>
<thead>
<tr>
<th>Age group</th>
<th>Men (n = 9203)</th>
<th>Women (n = 7818)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ST-T abn(^a)</td>
<td>No ST-T abn(^b)</td>
</tr>
<tr>
<td>40-64</td>
<td>9203</td>
<td>733</td>
</tr>
<tr>
<td>40-44</td>
<td>2306</td>
<td>120</td>
</tr>
<tr>
<td>45-49</td>
<td>2303</td>
<td>156</td>
</tr>
<tr>
<td>50-54</td>
<td>1957</td>
<td>146</td>
</tr>
<tr>
<td>55-59</td>
<td>1589</td>
<td>159</td>
</tr>
<tr>
<td>60-64</td>
<td>1048</td>
<td>152</td>
</tr>
</tbody>
</table>

\(^a\)Persons with primary ST segment depression and/or T wave abnormality.
\(^b\)Age-adjusted rate.

However, for men the difference was almost four times greater. After multivariate adjustment (for age, diastolic pressure, serum cholesterol, cigarettes per day, diabetes, and baseline use of antihypertensive medication), 11.5 year CHD mortality remained higher for individuals of both sexes with ST-T abnormalities,
with much greater relative risk and absolute excess risk for men than for women (table 3).

The Cox risk ratios for ST-T abnormalities, age, and the major CHD risk factors and their p values for the two sexes are listed in table 4. ST-T abnormalities, age, diastolic pressure, serum cholesterol, cigarette smoking, and diabetes were significantly related to long-term CHD mortality in men. In women, age, diastolic pressure, serum cholesterol, cigarette smoking, and diabetes, but not ST-T abnormalities, were significantly related to CHD mortality.

In the Cox regression analysis for men and women combined, the interaction term between sex and ST-T abnormalities was tested to evaluate further the sex difference with respect to the prognostic significance of ST-T abnormalities. The Cox coefficient for this interaction term was of borderline significance (p = .09), indicating a sex difference in the relation of ST-T abnormalities to 11.5 year risk of death from CHD.

The age-adjusted Cox risk ratio for ST-T abnormalities was 3.4 for men and 1.8 for women (table 5). Both were statistically significant (p < .001 for men and p < .05 for women). The multivariate-adjusted risk ratio for ST-T abnormalities was 2.6 for men (p < .001), but only 1.4 (NS) for women. As a result of this sex difference with respect to impact of ST-T abnormalities on risk of death from CHD, the Cox risk ratio of male to female long-term CHD death was much higher for those with than those without ST-T abnormalities (table 5).

### Discussion

This large prospective study demonstrated a substantial sex difference in the independent prognostic importance of ST-T abnormalities. ST-T abnormalities

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**TABLE 3**

Eleven and one-half year CHD mortality rates by ST-T abnormalities and by sex in white men and women 40 to 64 years old at entry to the Chicago Heart Association Detection Project in Industry

<table>
<thead>
<tr>
<th>Group</th>
<th>Total No. of CHD deaths</th>
<th>Age-adjusted</th>
<th>Multivariate-adjusted&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>9203</td>
<td>342</td>
<td>37.2</td>
</tr>
<tr>
<td>ST-T abn&lt;sup&gt;b&lt;/sup&gt;</td>
<td>733</td>
<td>86</td>
<td>117.3</td>
</tr>
<tr>
<td>No ST-T abn&lt;sup&gt;c&lt;/sup&gt;</td>
<td>8470</td>
<td>256</td>
<td>30.2</td>
</tr>
<tr>
<td>Absolute excess risk</td>
<td>87.1</td>
<td>80.4</td>
<td>69.2</td>
</tr>
<tr>
<td>Relative risk</td>
<td>3.9</td>
<td>3.5</td>
<td>3.2</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>7818</td>
<td>75</td>
<td>9.6</td>
</tr>
<tr>
<td>ST-T abn&lt;sup&gt;b&lt;/sup&gt;</td>
<td>977</td>
<td>17</td>
<td>17.4</td>
</tr>
<tr>
<td>No ST-T abn&lt;sup&gt;c&lt;/sup&gt;</td>
<td>6841</td>
<td>58</td>
<td>8.5</td>
</tr>
<tr>
<td>Absolute excess risk</td>
<td>8.9</td>
<td>7.5</td>
<td>4.7</td>
</tr>
<tr>
<td>Relative risk</td>
<td>2.1</td>
<td>1.9</td>
<td>1.5</td>
</tr>
</tbody>
</table>

| Adjusted for age, diastolic pressure, serum cholesterol, cigarettes smoked per day, diabetes, and baseline use of antihypertensive medication.
| Persons with primary ST segment depression and/or T wave abnormality.
| Persons without primary ST segment depression or T wave abnormality.

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**TABLE 4**

Relationship of ST-T abnormalities and other traits to 11.5 year CHD mortality in white men and women 40 to 64 years old at entry to the Chicago Heart Association Detection Project in Industry by Cox regression analysis

<table>
<thead>
<tr>
<th>Variables</th>
<th>Risk ratio</th>
<th>p value</th>
<th>Risk ratio</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ST-T (yes vs no)</td>
<td>2.6</td>
<td>&lt;.001</td>
<td>1.4</td>
<td>.245</td>
</tr>
<tr>
<td>Age (per 10 yr)</td>
<td>2.2</td>
<td>&lt;.001</td>
<td>3.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>DBP (per 20 mm Hg)</td>
<td>1.7</td>
<td>&lt;.001</td>
<td>1.6</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Chol (per 40 mg/dl)</td>
<td>1.3</td>
<td>&lt;.001</td>
<td>1.3</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Cig/Day (per pack)</td>
<td>1.6</td>
<td>&lt;.001</td>
<td>3.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diabetes (yes vs no)</td>
<td>3.2</td>
<td>&lt;.001</td>
<td>3.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Anti-hp med (yes vs no)</td>
<td>1.5</td>
<td>&lt;.05</td>
<td>2.0</td>
<td>&lt;.05</td>
</tr>
</tbody>
</table>

ST-T = ST-T abnormalities; DBP = diastolic blood pressure; Chol = serum cholesterol; Cig/day = cigarettes smoked per day; Anti-hp med = antihypertensive medication.

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**TABLE 5**

Risk ratios of CHD death by Cox regression in white men and women 40 to 64 years old at entry to the Chicago Heart Association Detection Project in Industry

<table>
<thead>
<tr>
<th>Group</th>
<th>Age-adjusted</th>
<th>Multivariate-adjusted&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>ST-T abn&lt;sup&gt;b&lt;/sup&gt;/No ST-T abn&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>3.4&lt;sup&gt;d&lt;/sup&gt;</td>
<td>2.6&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Women</td>
<td>1.8&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1.4</td>
</tr>
<tr>
<td>Men/Women Total</td>
<td>4.2&lt;sup&gt;g&lt;/sup&gt;</td>
<td>3.8&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td>ST-T abn&lt;sup&gt;b&lt;/sup&gt;</td>
<td>6.9&lt;sup&gt;e&lt;/sup&gt;</td>
<td>5.8&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>No ST-T abn&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3.8&lt;sup&gt;e&lt;/sup&gt;</td>
<td>3.4&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Adjusted for age, diastolic blood pressure, serum cholesterol, cigarettes smoked per day, diabetes, and baseline use of antihypertensive medication.

<sup>b</sup>Persons with primary ST segment depression and/or T wave abnormality.

<sup>c</sup>Persons without primary ST segment depression and/or T wave abnormality.

<sup>d</sup>p < .001; <sup>e</sup>p < .05.
were associated with a significantly increased CHD mortality for both middle-aged men and women during an average of 11.5 years of follow-up. However, excess risk of death from CHD was much greater for men than women. Moreover, when baseline age and other major CHD risk factors were considered in multivariate analyses, ST-T abnormalities remained significantly related to CHD death in men but not in women.

Previous studies have dealt with the prognostic significance of ST-T abnormalities in men (including men with CHD) but few have presented data for men and women separately. The present cohort consisted of about 17,000 men and women, with more than 1700 cases of baseline ST-T abnormalities, the largest such sample to date. However, the numbers of coronary deaths were small in women, with consequent limitations in statistical power. This may account for the finding that the interaction term between sex and ST-T abnormalities was of only borderline significance.

The present study showed that the prevalence rate of primary ST-T abnormalities was significantly higher in middle-aged women than men. The difference was recorded in every age group. This finding is consistent with data from three previous population studies in the United States. These findings seem paradoxical in view of the much lower incidence of major CHD events in women than men in “western” populations. As the data from the present study show, the higher rate of ST-T abnormalities in middle-aged women than men is not attributable to the major CHD risk factors, since the status of women tended to be more favorable than that of men, at least with regard to blood pressure, cigarette use, and diabetes.

The reasons for the observed sex differential in predictive significance of ST-T abnormalities for subsequent CHD death are unknown. ST-T abnormalities may well reflect different proportions of various entities in men and women. ST-T abnormalities have been described in a number of situations besides coronary artery disease, including change in posture, hypertension, the hyperkinetic heart syndrome, abnormalities of left ventricular wall motion related to mitral valve prolapse, and imbalance of the neurovegetative system. Anxiety or emotion also can affect the resting electrocardiogram and myocardial sensitivity to circulating catecholamines and has been suggested as a possible mechanism for the occurrence of ST-T abnormalities. More women than men may have these conditions, which may be more or less innocuous in terms of risk of fatal CHD.

It has also been postulated that some women with abnormal ST-T waves have myocardial ischemia without significant coronary atherosclerosis. Possible mechanisms include abnormal oxyhemoglobin dissociation and small-vessel disease, perhaps related to estrogen-induced changes in the clotting mechanism or to changes in myocardial lactate metabolism. It may be that prognosis for individuals with such myocardial ischemia is different than that for those with ST-T related ischemia due to coronary atherosclerosis.

The findings in men support the long-held view that in a sizable proportion of men with positive ST-T findings, these reflect subclinical CHD, particularly since these changes are associated with higher levels of major risk factors and with higher long-term CHD mortality. On the other hand, the much weaker prognostic significance of ST-T abnormalities in women than men suggests that ST-T abnormalities reflect CHD for a much smaller proportion of women with these findings, i.e., they are more often signs of prognostically nonsignificant or less significant processes than latent CHD.

Despite these findings, criteria for the normal electrocardiogram, including ST segment and T wave criteria, remain for the present the same for men and women, since the exact nature and range of the sex differences in normal ECG variation are not known. Therefore, with use of the same criteria for ST segment depression and T wave abnormality for both sexes, it may be that more women than men are misclassified as “abnormal.” Further research is needed to clarify whether — as implied by the results of the present study — different criteria for ST-T abnormalities may be appropriate for the two sexes.

We are pleased to acknowledge the cooperation of the Chicago organizations and business institutions and their employees who participated in the Chicago Heart Association Detection Project in Industry (CHA). Acknowledgment is also gratefully extended to all those involved in the Project: Louis de Boer, Raymond Restivo, Kay Westfall, and Sue Shekelle of the Chicago Heart Association, the project staffs, and the many CHA volunteers.

References

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