Ability of Exercise Testing to Predict Cardiovascular and All-Cause Death in Asymptomatic Women
A 20-Year Follow-up of the Lipid Research Clinics Prevalence Study

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Cardiovascular Disease claims the life of 1 of every 2 women in the United States, with most sudden deaths in women occurring in those with no previous symptoms. Identifying asymptomatic women who are at increased risk and who may benefit from aggressive primary prevention has the potential to reduce cardiovascular morbidity and mortality in women. It is controversial whether exercise testing should be used to screen asymptomatic women for cardiovascular risk. While several studies have found certain exercise test variables (eg, reduced exercise capacity and ischemic ST-segment depression) to be associated with increased mortality in healthy men, it is not known if these have similar prognostic value in women. It is also unclear how other exercise test variables compare with ST-segment depression as predictors of mortality.

We investigated the role of exercise treadmill testing in predicting cardiovascular and all-cause death in a population-based cohort of asymptomatic women. We aimed to identify whether exercise test variables related to ischemia, fitness, and autonomic function were independent predictors of increased risk of all-cause or cardiovascular death and whether there were sex-related differences in the prognostic value of these exercise test variables.

Context The value of exercise testing in women has been questioned.

Objective To determine the prognostic value of exercise testing in a population-based cohort of asymptomatic women followed up for 20 years.


Participants A total of 2994 asymptomatic North American women, aged 30 to 80 years, without known cardiovascular disease.

Main Outcome Measures Cardiovascular and all-cause mortality.

Results There were 427 (14%) deaths during 20 years of follow-up, of which 147 were due to cardiovascular causes. Low exercise capacity, low heart rate recovery (HRR), and not achieving target heart rate were independently associated with increased all-cause and cardiovascular mortality. There was no increased cardiovascular death risk for exercise-induced ST-segment depression (age-adjusted hazard ratio, 1.02; 95% confidence interval [CI], 0.57-1.80; P = .96). The age-adjusted hazard ratio for cardiovascular death for every metabolic equivalent (MET) decrement in exercise capacity was 1.20 (95% CI, 1.18-1.30; P < .001); for every 10 beats per minute decrement in HRR, the hazard ratio was 1.36 (95% CI, 1.19-1.55; P < .001). After adjusting for multiple other risk factors, women who were below the median for both exercise capacity and HRR had a 3.5-fold increased risk of cardiovascular death (95% CI, 1.57-7.86; P = .002) compared with those above the median for both variables. Among women with low risk Framingham scores, those with below median levels of both exercise capacity and HRR had significantly increased risk compared with women who had above median levels of these 2 exercise variables, 44.5 and 3.5 cardiovascular deaths per 10 000 person-years, respectively (hazard ratio for cardiovascular death, 12.93; 95% CI, 5.62-29.73; P < .001).

Conclusion The prognostic value of exercise testing in asymptomatic women derives not from electrocardiographic ischemia but from fitness-related variables.

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METHODS
Study Population
The study participants were enrolled in the Lipid Research Clinics Prevalence Study, which has been previously described. Briefly, a 2-stage screening procedure was used. From 1972-1976, individuals were screened at 10 centers in North America (visit 1). A sample consisting of 15% of eligible participants randomly selected from visit 1 and all the visit 1 participants with elevated lipid levels were invited back to visit 2 for baseline history, physical examination, fasting blood samples, and exercise tests. The women from the random sample constituted 62% of the study cohort, similar to the proportion in the original cohort at visit 2. Participants were followed up annually for vital status ascertainment until death or end of follow-up (December 31, 1995). Until 1988, deaths were identified by mail or telephone contact and confirmed using death certificates, interviews with next-of-kin or other witnesses, and review of medical records. Cause of death was classified by a committee of cardiologists masked to the identity of the deceased. From 1988-1995, deaths were identified from death certificates by trained nosologists using the National Death Index (1988-1991) and the Epidemiology Research Index (1992-1995). Participants were ineligible for exercise testing at baseline if they were pregnant, had significant cardiovascular disease, or were deemed ineligible for exercise testing by the study physicians. Of the 4006 women who came to visit 2 and were followed up, 630 did not have a baseline exercise test done. Another 382 were excluded from this analysis because they were younger than 30 years or older than 80 years; had a history of angina, claudication, myocardial infarction, stroke, heart surgery, left ventricular hypertrophy, digoxin use; exercise duration less than 1 minute; a modified Bruce exercise test; or were lost to follow-up (3 women). Thus, this study included 2994 asymptomatic women who were followed up until their death or end of follow-up (December 31, 1995). Participants gave informed written consent and the study had institutional review board approval from the University of Maryland and the Johns Hopkins Medical Institutions.

Exercise Testing
At visit 2, participants underwent exercise testing using a Bruce treadmill protocol (no cool-down period). The test was terminated when a target heart rate of 90% or more of maximal predicted heart rate for age and physical activity level was attained. Target heart rates were predetermined by the investigators based on age and baseline physical activity with slightly lower target rates (approximately 5/min lower) for physically active individuals. The test was stopped prematurely if the participant was unable or refused to continue; developed significant arrhythmias, hypertension, electrocardiographic changes or angina; or due to technical difficulties. Exercise electrocardiograms were read by 2 trained coders and reviewed by a supervisor using a carefully defined visual coding system with an internal quality control system at a central coding center. Discrepancies between the coders were adjudicated by the supervisor in consultation with 1 of 2 cardiologists. The exercise electrocardiogram was also computer analyzed, and any differences between visual and computer coding were adjudicated by the supervisor and the cardiologists.

Definition of Clinical Variables
ST-segment depression was defined as at least 1.0 mm horizontal or downsloping depression at 0.08 seconds after the J point in the lead with the greatest abnormality (X, Y, Z [orthogonal leads], V1, V5, V6) in the last stage of exercise or recovery. To compare with previous studies,15-17 exercise-induced ventricular arrhythmia was defined as multifocal or at least 10% premature ventricular contractions in the last stage of exercise or recovery, or if the test was terminated due to ventricular tachycardia. Target heart rate was not attained if the participants failed to reach 90% or more of their maximal predicted heart rate for age and baseline physical activity. Peak exercise capacity was estimated from treadmill time and expressed in metabolic equivalents (METs).18 Heart rate recovery (HRR) was defined as peak heart rate minus heart rate at 2 minutes postexercise (subjects were seated in a chair immediately after exercise).

Definition of Exercise Test Variables
Target heart rate was estimated from treadmill time and expressed in metabolic equivalents (METs). Heart rate recovery (HRR) was defined as peak heart rate minus heart rate at 2 minutes postexercise (approximately 5/min lower) for physically active individuals. The test was stopped prematurely if the participant was unable or refused to continue; developed significant arrhythmias, hypertension, electrocardiographic changes or angina; or due to technical difficulties. Exercise electrocardiograms were read by trained coders and reviewed by a supervisor using a carefully defined visual coding system with an internal quality control system at a central coding center. Discrepancies between the coders were adjudicated by the supervisor in consultation with 1 of 2 cardiologists. The exercise electrocardiogram was also computer analyzed, and any differences between visual and computer coding were adjudicated by the supervisor and the cardiologists.
15% to 25% as intermediate risk, and more than 25% as high risk.

**Statistical Methods**

Statistical analyses were performed using STATA, 2001. Survival analysis was done with Kaplan-Meier curves and log-rank tests across quintiles. Mortality rates were calculated as the number of deaths divided by person-years of follow-up. Age-adjusted Cox proportional hazards models that included the variable and age in years, and multivariable models that adjusted for other covariates, were used to estimate hazard ratios and 95% confidence intervals (CIs) for the association of variables with time to death. The proportional hazard assumption was satisfied using Schoenfeld residuals.

In the final multivariable models, the variables that were included in addition to the exercise test variables were age, smoking, diabetes, family history of premature coronary heart disease, obesity, high LDL cholesterol level, low HDL cholesterol level, high triglyceride level, and hypertension. Cardiovascular risk factors were assessed both as continuous and categorical variables. When cardiovascular risk factors were included in the models as continuous variables, no change was noted in the coefficients compared with models that had categorical variables. The addition of covariates for study site, regular exercise, and the use of lipid-lowering medications also did not change the values of the coefficients for the exercise test variables, nor were these additional covariates associated with mortality. Therefore, the final models did not include these covariates.

Peak exercise capacity and HRR were assessed as continuous variables, quintiles, and categories (≤study median vs >median). Heart rate recovery was also examined using a cut-off value (abnormal if <22/min) that has been associated with increased mortality in previous studies. We tested for interaction with interaction terms and stratification. Stepwise forward and backward Cox regression analyses (at the .05 significance level) were used to statistically select which exercise test variables were independent predictors of risk. All reported P values were 2-sided.

**RESULTS**

During a mean (SD) follow-up of 20.3 (3.9) years of the 2994 women, there were 427 (14%) deaths from any cause, including 147 cardiovascular deaths.

### Table 1. Baseline Demographic, Clinical, and Exercise Test Characteristics According to Exercise Capacity and Heart Rate Recovery

<table>
<thead>
<tr>
<th>Variable</th>
<th>High METs/ High HRR (n = 822)</th>
<th>Low METs/ High HRR (n = 644)</th>
<th>High METs/ Low HRR (n = 579)</th>
<th>Low METs/ Low HRR (n = 940)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic and clinical†‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause death, No. (%)</td>
<td>39 (5)</td>
<td>78 (12)</td>
<td>52 (9)</td>
<td>257 (27)</td>
</tr>
<tr>
<td>Cardiovascular death, No. (%)</td>
<td>7 (1)</td>
<td>19 (3)</td>
<td>17 (3)</td>
<td>103 (11)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>42 (9)</td>
<td>47 (11)</td>
<td>44 (10)</td>
<td>52 (12)</td>
</tr>
<tr>
<td>White, No. (%)</td>
<td>780 (95)</td>
<td>595 (93)</td>
<td>553 (96)</td>
<td>899 (96)</td>
</tr>
<tr>
<td>Systolic blood pressure, mean (SD), mm Hg</td>
<td>114 (15)</td>
<td>122 (18)</td>
<td>120 (17)</td>
<td>129 (19)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mean (SD), mm Hg</td>
<td>74 (10)</td>
<td>78 (10)</td>
<td>77 (10)</td>
<td>80 (10)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>24.0 (4.0)</td>
<td>25.5 (5.0)</td>
<td>24.1 (4.1)</td>
<td>25.9 (5.1)</td>
</tr>
<tr>
<td>Total cholesterol ≥240 mg/dL (≥6.22 mmol/L), No. (%)</td>
<td>200 (24)</td>
<td>211 (33)</td>
<td>189 (33)</td>
<td>402 (43)</td>
</tr>
<tr>
<td>LDL cholesterol ≥160 mg/dL (≥4.14 mmol/L), No. (%)</td>
<td>204 (25)</td>
<td>208 (32)</td>
<td>193 (33)</td>
<td>397 (42)</td>
</tr>
<tr>
<td>HDL &lt;40 mg/dL (&lt;1.04 mmol/L), No. (%)</td>
<td>68 (8)</td>
<td>56 (9)</td>
<td>79 (14)</td>
<td>120 (13)</td>
</tr>
<tr>
<td>Triglycerides ≥200 mg/dL (≥2.66 mmol/L), No. (%)</td>
<td>58 (7)</td>
<td>79 (12)</td>
<td>63 (11)</td>
<td>159 (17)</td>
</tr>
<tr>
<td>Diabetes, No. (%)</td>
<td>8 (1)</td>
<td>10 (2)</td>
<td>17 (3)</td>
<td>49 (5)</td>
</tr>
<tr>
<td>Current smoking, No. (%)</td>
<td>280 (34)</td>
<td>172 (27)</td>
<td>240 (41)</td>
<td>322 (34)</td>
</tr>
<tr>
<td>Regular exercise, No. (%)</td>
<td>160 (19)</td>
<td>77 (12)</td>
<td>71 (12)</td>
<td>79 (9)</td>
</tr>
<tr>
<td>Family history, No. (%)</td>
<td>178 (22)</td>
<td>107 (17)</td>
<td>111 (19)</td>
<td>160 (17)</td>
</tr>
<tr>
<td>Exercise test:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak exercise capacity, mean (SD), METs</td>
<td>9.3 (1.2)</td>
<td>5.9 (1.4)</td>
<td>9.2 (1.2)</td>
<td>5.4 (1.6)</td>
</tr>
<tr>
<td>Resting heart rate, mean (SD), beats/min</td>
<td>80 (11)</td>
<td>83 (13)</td>
<td>85 (12)</td>
<td>90 (14)</td>
</tr>
<tr>
<td>Maximal heart rate, mean (SD), beats/min</td>
<td>170 (8)</td>
<td>166 (14)</td>
<td>166 (11)</td>
<td>156 (18)</td>
</tr>
<tr>
<td>HRR, mean (SD), beats/min</td>
<td>66 (8)</td>
<td>65 (8)</td>
<td>48 (7)</td>
<td>44 (9)</td>
</tr>
<tr>
<td>Target heart rate not attained, No. (%)</td>
<td>171 (21)</td>
<td>205 (32)</td>
<td>206 (36)</td>
<td>508 (54)</td>
</tr>
<tr>
<td>Ventricular arrhythmia, No. (%)</td>
<td>39 (5)</td>
<td>46 (7)</td>
<td>29 (5)</td>
<td>114 (12)</td>
</tr>
<tr>
<td>ST depression ≥1.0 mm, No. (%)</td>
<td>27 (3)</td>
<td>42 (7)</td>
<td>18 (3)</td>
<td>53 (6)</td>
</tr>
</tbody>
</table>

Abbreviations: HDL, high-density lipoprotein; HRR, heart rate recovery; LDL, low-density lipoprotein; METs, metabolic equivalents.

*High and low METs is exercise capacity above or below the study median (7.5 METs). HRR is heart rate recovery above or below the study median (55/min). Numbers may not add up due to rounding.

†Regular exercise is self-reported participation in regular strenuous activity or hard labor. Family history is premature coronary heart disease in a parent or sibling. Target heart rate not attained is maximal rate less than 90% of maximal predicted rate for age and physical activity. Body mass index calculated as weight in kilograms divided by the square of height in meters.

‡Ventricular arrhythmia is multifocal or at least 10% premature ventricular contractions in exercise or recovery, or reason for test termination. ST depression is at least 1 mm of horizontal or downsloping depression in exercise or recovery, METs was available for all 2994 women, but HRR was not available for 9 women, 1 of whom died.
mortality for decreasing quintiles of exercise capacity and HRR (P values from log-rank tests .001 across quintiles for both variables). Similar results were obtained for survival free of cardiovascular death.

**Age-Adjusted Predictors of Mortality**

After age adjustment, the effects of exercise capacity, HRR, not achieving target heart rate, and exercise-induced ventricular arrhythmia on cardiovascular and all-cause mortality were similar in magnitude to the effects of traditional cardiovascular risk factors (TABLE 2). Neither total nor LDL cholesterol level predicted cardiovascular death after adjusting for age, similar to previous results in women from this cohort. The age-adjusted hazard ratio for cardiovascular death for every MET decrement in exercise capacity was 1.20 (95% CI, 1.18-1.30), and for every 10/min-decrement in HRR, 1.36 (95% CI, 1.18-1.30). For both variables, there was a strong and graded association between decreasing quintiles and age-adjusted risk of cardiovascular and all-cause death (P values for trend <.001).

In contrast, exercise-induced ST-segment depression of at least 1 mm did not predict cardiovascular death (age-adjusted hazard ratio, 1.02; 95% CI, 0.57-1.80); neither did ST-segment depression of at least 2 mm (age-adjusted hazard ratio, 0.97; 95% CI, 0.14-6.93). In the subgroup of women who were older than 55 years at baseline (n = 714), there were 104 of the 147 cardiovascular deaths during follow-up, with no predictive value for ST-segment depression (age-adjusted hazard ratio, 1.03; 95% CI, 0.55-1.93). To compare with earlier published results on the men in the Lipid Research Clinics study, we analyzed the data at 10-year follow-up and again found that ST-segment depression was not associated with increased risk.

**Multivariable Predictors of Mortality**

We analyzed the prognostic value of exercise test variables, considered one at a time, after adjusting simultaneously for cardiovascular risk factors (age, current smoking, diabetes, family history of premature coronary heart disease, obesity, high LDL cholesterol level, low HDL cholesterol level, high triglyceride level, and hypertension). When risk factors were included in these models.
as continuous variables, similar results were obtained. Independent exercise test predictors of cardiovascular death were exercise capacity, HRR, not achieving target heart rate, and ventricular arrhythmia (Table 3). ST-segment depression was not associated with increased risk.

In a multivariable model for all-cause mortality that included both peak exercise capacity and HRR together in the same model with all the cardiovascular risk factors, there were trivial changes in the hazard ratios for both variables and each remained independently predictive of mortality (P < .001 for exercise capacity and P = .002 for HRR). When the study population was divided into 4 groups based on the median values for exercise capacity and HRR (Table 4), women who were below the median with respect to both exercise capacity and HRR had a 3.5-fold increased risk of cardiovascular death compared with women who were above the median for both variables, after controlling for cardiovascular risk factors.

Stepwise forward and backward Cox regression analysis confirmed that exercise capacity and HRR were the only 2 exercise test variables that were statistically selected as independent predictors in the same model after accounting for cardiovascular risk factors. There was no interaction between exercise capacity and HRR. There were no interactions between HRR or peak exercise capacity and any cardiovascular risk factor (including menopause status and sex) for cardiovascular or all-cause mortality.

In contrast, there was a highly statistically significant interaction between sex and ST-segment depression for all-cause mortality (P < .001), and a significant interaction for cardiovascular mortality (P = .02). Identical analyses on the 3769 asymptomatic men who were followed up for 20 years in this cohort showed that the increased risk of exercise-induced ST-segment depression that was found at 8-year follow-up13 persisted at 20 years. Despite a similarly low prevalence of ST-segment depression in both men and women, ST-segment depression of at least 1 mm in men was predictive of both cardiovascular and all-cause mortality after multivariable adjustment for cardiovascular risk factors (adjusted hazard ratios and 95% CIs for cardiovascular death, 1.92 [1.31-2.82]; and for all-cause death, 1.44 [1.09-1.90]).

**Risk Stratification by Exercise Testing and Framingham Risk Scores**

Using their baseline Framingham risk scores, 95% of the women were at low risk, with 4% at intermediate and 1% at high risk. Women with low risk Framingham scores (n=2817) were further subdivided into 3 categories based on their exercise capacity and HRR levels: greater than the median in the 2 exercise test variables (group 1, n=811); greater than the median in 1 of the 2 variables (group 2, n=1168); and greater than the median in the 2 variables (group 3, n=838). Cardiovascular mortality rates in these 3 groups, re-

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**Table 2. Age-Adjusted Risk of Cardiovascular and All-Cause Death by Clinical and Exercise Test Variables**

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Deaths</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>84</td>
<td>3.45 (2.07-5.73)</td>
<td>.001</td>
</tr>
<tr>
<td>Current smoking</td>
<td>1018</td>
<td>2.37 (1.68-3.36)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Total cholesterol ≥240 mg/dL (≥6.22 mmol/L)</td>
<td>1004</td>
<td>1.24 (0.89-1.72)</td>
<td>.20</td>
</tr>
<tr>
<td>LDL cholesterol ≥160 mg/dL (≥4.14 mmol/L)</td>
<td>1004</td>
<td>1.26 (0.91-1.74)</td>
<td>.20</td>
</tr>
<tr>
<td>Triglycerides ≥200 mg/dL (≥2.26 mmol/L)</td>
<td>361</td>
<td>2.37 (1.64-3.40)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HDL cholesterol &lt;40 mg/dL (&lt;1.04 mmol/L)</td>
<td>323</td>
<td>1.91 (1.22-2.98)</td>
<td>.004</td>
</tr>
<tr>
<td>Hypertension</td>
<td>714</td>
<td>1.82 (1.29-2.56)</td>
<td>.001</td>
</tr>
<tr>
<td>Body mass index ≥30†</td>
<td>390</td>
<td>1.79 (1.19-2.69)</td>
<td>.005</td>
</tr>
</tbody>
</table>

| Exercise test | Exercise capacity | Categorical (≤median) | 1589 | 123 | 2.04 (1.29-3.25) | .003 |
| | Continuous (per MET decrement) | . . . | . . . | 1.20 (1.18-1.30) | <.001 |
| **HRR** | | Categorical (<22/min) | 21 | 4 | 3.02 (1.11-8.18) | .03 |
| | Continuous (≤median) | 1519 | 120 | 2.85 (1.85-4.39) | <.001 |
| Target heart rate not attained | 1091 | 1.72 (1.19-2.48) | .004 |
| Ventricular arrhythmia | 229 | 1.53 (1.00-2.33) | .05 |
| ST depression ≥1.0 mm | 141 | 1.02 (0.57-1.80) | .96 |

*Abbreviations: CI, confidence interval; HDL, high-density lipoprotein; HRR, heart rate recovery; LDL, low-density lipoprotein; MET, metabolic equivalent.
*Hazard ratios and 95% CIs are from Cox proportional hazards models that included the variable and age (years), comparing women with the variable to those without it. For exercise capacity and HRR, age-adjusted hazard ratios are additionally shown for every MET decrement in exercise capacity and for every 10/min-decrement in HRR.
†Calculated as weight in kilograms divided by the square of height in meters.

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respectively, were 3.5, 13.3, and 44.5 deaths per 10000 person-years of follow-up. Using group 1 as the reference, the hazard ratios for cardiovascular death for groups 2 and 3 were 3.76 (95% CI, 1.57-9.00; P=.003) and 12.93 (95% CI, 5.62-29.73; P<.001), respectively, and for all-cause death 2.15 (95% CI, 1.49-3.10; P<.001) and 5.69 (95% CI, 4.03-8.05; P<.001), respectively. While there were few women with intermediate Framingham risk scores, 18 (78%) of the 23 cardiovascular deaths in this group occurred in women with below median values for both exercise capacity and HRR. There were only 28 women and 10 cardiovascular deaths in women with high risk Framingham scores, and all 10 deaths occurred in women with below median values for both exercise test variables.

**COMMENT**

In our population-based cohort of asymptomatic North American women, exercise testing clearly discriminated mortality risk using exercise variables other than ST-segment responses. Exercise capacity and heart rate responses during exercise and recovery were strong, graded, and independent predictors of cardiovascular and all-cause mortality, while exercise-induced ST-segment depression was not. Failure to achieve target heart rate and ventricular arrhythmia were also predictors of poor prognosis.

Our study has several important new findings. First, exercise-induced ST-segment depression had no predictive value in women, in contrast to its increased risk in men as reported previously and confirmed in our analysis. Even in older women, there was no increased risk associated with ST-segment depression, despite enrichment of the sample with hyperlipidemic women. The hazard ratio for ST-segment depression with cardiovascular mortality was a trivial and nonsignificant 1.02. Thus, a larger sample size or a greater prevalence of ST-segment depression is unlikely to show a substantial effect on risk. The effect of gender on the prognostic value of ST-segment depression is intriguing in light of previous studies showing gender differences in the diagnostic accuracy of ST-segment changes. Mechanisms that may contribute to this remain unclear and may be related to differential effects of estrogens and androgens on the ST-segment and QT interval or differences in endothelial dysfunction.

Second, easily obtained exercise testing measures, specifically exercise capacity and HRR, had powerful prognostic value for both cardiovascular and all-cause death. Our study underscores the independent value of exercise capacity in predicting cardiovascular and overall risk in asymptomatic women, as seen earlier in men and in other studies with fewer women and shorter follow-up. Moreover, our results confirm the independent effect of abnormal HRR found in other studies and suggest that low levels of both HRR and exercise capacity have significantly worse prognosis, even after accounting for age and other risk factors. Research on the role of the autonomic nervous system, inflammation, insulin resistance, genetics, and other novel risk factors may provide insight into the mechanisms by which fitness and autonomic function may influence risk.

Third, there is great public health interest in cost-effective and readily available tests that can predict cardiovascular risk in asymptomatic women. Since nearly two thirds of women who die suddenly have no previous symptoms, our results support the potential role of exercise treadmill testing for further risk stratification of asymptomatic women.
atic women with low or intermediate Framingham risk scores. In addition, we recommend the promotion of better fitness levels for women regardless of their Framingham risk. Physical inactivity is currently a major public health problem and is more prevalent in women than men. While increased physical activity improves cardiovascular risk profiles, our study suggests that women may benefit from higher fitness levels independent of changes in weight, blood pressure, or lipid levels.

One limitation to our study was that exercise capacity was estimated from near-maximal exercise tests that were not necessarily symptom limited. This may have inappropriately reduced the estimates of peak exercise capacity in some women and possibly underestimated the strength of the association of peak exercise capacity with mortality. In addition, we cannot distinguish effects on incidence from effects on survival since data on incident myocardial infarction or cardiovascular disease were not obtained. However, there are no studies that suggest that fitness is related only to survival after the clinical manifestation of cardiovascular disease. Although changes in classification of causes of death with possible nondifferential misclassification may have occurred during our long study period, this would be expected to underestimate the strength of the association between exercise test variables and mortality. Our study sample included few nonwhites and many with lipid abnormalities, but the prognostic value of exercise capacity and HRR was similar in subgroups with normal and elevated lipid levels. The extent to which these exercise test measures of risk can be modified is also unclear, although exercise capacity may be improved with moderate regular physical activity by about 15% to 30% in a period of several months. Finally, the value of exercise testing to screen asymptomatic populations for the purpose of reducing cardiovascular or overall mortality has not yet been studied in large randomized trials.

In summary, the association of exercise capacity and HRR with cardiovascular and all-cause mortality was strong, consistent, graded, and independent, while exercise-induced ST-segment depression carried no increased risk in this large population-based cohort of women. Our findings support the potential use of exercise testing as a risk-stratification tool for primary prevention in asymptomatic women, incremental to the traditional cardiovascular risk factors.

Author Contributions: Study concept and design: Mora, Cui, Flaws, Blumenthal. Acquisition of data: Mora, Cui, Whiteman. Analysis and interpretation of data: Mora, Redberg, Cui, Whiteman, Flaws, Sharrett, Blumenthal. Drafting of the manuscript: Mora, Blumenthal. Critical revision of the manuscript for important intellectual content: Mora, Redberg, Cui, Whiteman, Flaws, Sharrett, Blumenthal. Statistical expertise: Mora, Cui, Whiteman, Sharrett, Blumenthal. Obtained funding: Mora, Blumenthal. Administrative, technical, or material support: Mora, Flaws, Blumenthal. Study supervision: Mora, Redberg, Sharrett, Blumenthal.

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REFERENCES
EXERCISE TESTING IN WOMEN


