

ORIGINAL ARTICLE

The Prognostic Value of a Nomogram for Exercise Capacity in Women

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ABSTRACT

BACKGROUND

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Recent studies have demonstrated that exercise capacity is an independent predictor of mortality in women. Normative values of exercise capacity for age in women have not been well established. Our objectives were to construct a nomogram to permit determination of predicted exercise capacity for age in women and to assess the predictive value of the nomogram with respect to survival.

METHODS

A total of 5721 asymptomatic women underwent a symptom-limited, maximal stress test. Exercise capacity was measured in metabolic equivalents (MET). Linear regression was used to estimate the mean MET achieved for age. A nomogram was established to allow the percentage of predicted exercise capacity to be estimated on the basis of age and the exercise capacity achieved. The nomogram was then used to determine the percentage of predicted exercise capacity for both the original cohort and a referral population of 4471 women with cardiovascular symptoms who underwent a symptom-limited stress test. Survival data were obtained for both cohorts, and Cox survival analysis was used to estimate the rates of death from any cause and from cardiac causes in each group.

RESULTS

The linear regression equation for predicted exercise capacity (in MET) on the basis of age in the cohort of asymptomatic women was as follows: predicted MET = 14.7 - (0.13 × age). The risk of death among asymptomatic women whose exercise capacity was less than 85 percent of the predicted value for age was twice that among women whose exercise capacity was at least 85 percent of the age-predicted value (P < 0.001). Results were similar in the cohort of symptomatic women.

CONCLUSIONS

We have established a nomogram for predicted exercise capacity on the basis of age that is predictive of survival among both asymptomatic and symptomatic women. These findings could be incorporated into the interpretation of exercise stress tests, providing additional prognostic information for risk stratification.

EXERCISE CAPACITY IS AN INDEPENDENT predictor of the risk of death and cardiac events among asymptomatic women and men.¹⁻⁵ Exercise capacity may be defined as the maximal oxygen uptake for a given workload^{6,7} and can be expressed in metabolic equivalents (MET), or multiples of the basal rate of oxygen consumption when a person is at rest (3.5 ml per kilogram of body weight per minute for an average adult).⁸ Exercise capacity can be estimated by performing a symptom-limited stress test.

Exercise capacity varies with age, sex, and health. A number of studies have established that there is a negative linear relationship between exercise capacity and age in men, and a nomogram has been developed for men that estimates the percentage of predicted exercise capacity for a given age.^{6,7,9-11} Few studies have evaluated exercise capacity in women, and to date, no standard for age-related declines in physical fitness has been established for women.

We had two goals in conducting this study. The first was to create a simple nomogram for women to allow the conversion of the MET value achieved on a stress test into a percentage of the predicted exercise capacity for any age, on the basis of findings in a population of asymptomatic women. The second goal was to assess the usefulness of the nomogram in predicting survival among both asymptomatic women and a referral population of women with cardiovascular symptoms in order to determine its usefulness in clinical practice.

METHODS

ASYMPTOMATIC POPULATION

The asymptomatic population came from the St. James Women Take Heart Project. This cohort has previously been described.¹ Briefly, in 1992 volunteers were solicited from the Chicago metropolitan area to participate in a study of heart disease in women. The project was approved by the institutional review board of St. James Hospital and Rush-Presbyterian-St. Luke's Medical Center, with written informed consent obtained from all study participants.

Inclusion criteria for the study cohort were an age of at least 35 years and the ability to walk on a treadmill at a moderate pace. Women were excluded if they were pregnant, had typical anginal symptoms or any history of cardiac disease (including previous myocardial infarction, documented coro-

nary artery disease, heart failure, or valvular heart disease), weighed more than 148 kg (325 lb), had a baseline blood pressure of 170/110 mm Hg or higher, or had incomplete data concerning cardiac risk factors. Members of the cohort were classified as sedentary or active on the basis of their response to one question: Do you have a regular (exercise) training program?

REFERRAL POPULATION

The referral population came from the Economics of Noninvasive Diagnosis Study, which has been described previously.^{12,13} Briefly, this cohort was composed of consecutive women from six medical centers who were referred between 1990 and 1995 for a symptom-limited exercise stress test with the use of the Bruce protocol¹⁴ for the evaluation of suspected coronary disease. Women were excluded if they had recently been hospitalized for unstable angina, myocardial infarction, or coronary revascularization. The study was approved by the institutional review board at each of the six participating centers. For all but one site, written informed consent for follow-up was obtained at the time of the initial procedure. For the remaining site, the requirement for informed consent was waived by the institutional review board because the data were from a previously approved database.

EXERCISE TREADMILL TESTING

All participants underwent a symptom-limited treadmill test according to the Bruce protocol.¹⁴ The test was discontinued in the event of limiting symptoms (angina, dyspnea, or fatigue), abnormalities of rhythm or blood pressure, or marked and progressive ST-segment deviation. Target heart rates were not used as a predetermined end point.

In the asymptomatic group, some participants underwent stress testing according to a modified Bruce protocol. These women were excluded from the analysis, because submaximal exercise testing does not accurately reflect physical fitness in the way that maximal exercise testing does.

EXERCISE CAPACITY

The estimated exercise capacity was measured in MET^{6,7} as defined above. The estimate was based on the speed and grade of the treadmill.¹⁵

FOLLOW-UP DATA

The number of deaths from any cause in the asymptomatic cohort was determined by searching the

National Death Index to identify deaths and causes of death from the time of the baseline evaluation in 1992 through the end of 2000. Follow-up information was obtained on the referral (symptomatic) population through 2000 during a clinic visit or telephone interview. Deaths were identified and the cause of death was classified after a review of death certificates by an independent reviewer who was unaware of the women's clinical history and stress-testing data.

STATISTICAL ANALYSIS

The MET achieved was determined from the final speed and grade of the treadmill, as defined for the Bruce protocol.¹⁵ Using the asymptomatic population, we calculated the linear regression of exercise

capacity (in MET) on age; no evidence of nonlinearity was found. The calculated value from the regression equation for age was defined as 100 percent of the age-predicted exercise capacity.

For each participant in both groups, the percentage of the predicted exercise capacity achieved for age was then calculated with the use of the following equation: percentage of predicted exercise capacity achieved for age = (observed MET ÷ age-predicted MET) × 100. A nomogram to determine the percentage of predicted exercise capacity for age was constructed with the use of the linear regression equation for the asymptomatic cohort. Similarly, separate nomograms were also created for both the active and sedentary groups.

The correlation of the percentage of predicted exercise capacity for any given age with subsequent survival was calculated in both groups. The rates of death from any cause and from cardiac causes were analyzed for both populations with the use of univariate Cox proportional-hazards models, on the basis of the deviation from the predicted normal value of exercise capacity for age. From the Cox models, the predicted rates of death from cardiac causes were plotted against the ratio of observed exercise capacity to expected exercise capacity, and an r^2 statistic was calculated. Annualized death rates and rates of death from cardiac causes were calculated by dividing the predicted death rates from the Cox model by the length of follow-up. All analyses were performed with the use of STATA software (version 8.0) or SPSS software (version 12.0). A two-sided P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

A total of 5721 asymptomatic women and 4471 symptomatic women met the study-specific inclusion criteria.^{1,12,13,16} The characteristics of the two cohorts are shown in Table 1. The asymptomatic cohort was younger than the symptomatic cohort and was predominantly white (85 percent). Although the majority of the symptomatic women were white, almost a third were black. Fewer asymptomatic women had a history of hypertension or diabetes. Atypical symptoms accounted for only a quarter of the symptoms in the symptomatic cohort. The asymptomatic women had a higher mean exercise capacity and a lower overall mortality rate during the follow-up period than did the symptomatic women.

Characteristic	Asymptomatic Women (N=5721)	Symptomatic Women (N=4471)
Age — yr		
Mean	52±11	61±12
Range	35–86	34–93
Race — %†		
White	85	62
Black	9	28
Other	6	10
Risk factors — %†		
Hypertension	17	49
Diabetes	5	22
Current or former smoker	21	25
Family history of CAD	44	35
Hypercholesterolemia	17	12
Typical angina — %	—	58
Atypical or nonanginal CP — %	—	25
Dyspnea or symptoms of CHF — %	—	17
Exercise capacity — MET		
Peak	8.0±2.7	6.9±3.4
Range	1.4–20.0	1.2–17.4
Death — no. (%)		
Any cause	180 (3)	537 (12)
Cardiac causes	58 (1)	45 (1)
Duration of follow-up — yr	8.4±0.7	5.3±2.1

* Plus-minus values are means ±SD. CAD denotes coronary artery disease, CP chest pain, and CHF congestive heart failure.

† Race and risk factors were self-reported.

PREDICTED EXERCISE CAPACITY

The relationship between exercise capacity and age in the cohort of 5721 asymptomatic women was linear. Regression analysis of exercise capacity for age yielded the following equation: predicted MET=14.7-(0.13×age), with an age-adjusted SD of 2.3 (r= -0.51, P<0.001).

The same regression analysis was stratified according to the level of reported activity. A total of 212 women did not respond to the exercise question and were excluded from this analysis. For the active subgroup of 866 women, the regression equation was as follows: predicted MET=17.9-(0.16×age), with an age-adjusted SD of 2.4 (r= -0.59, P<0.001). For the sedentary subgroup of 4643 women, the regression equation was as follows: predicted MET=14.0-(0.12×age), with an age-adjusted SD of 2.2 (r= -0.49, P<0.001).

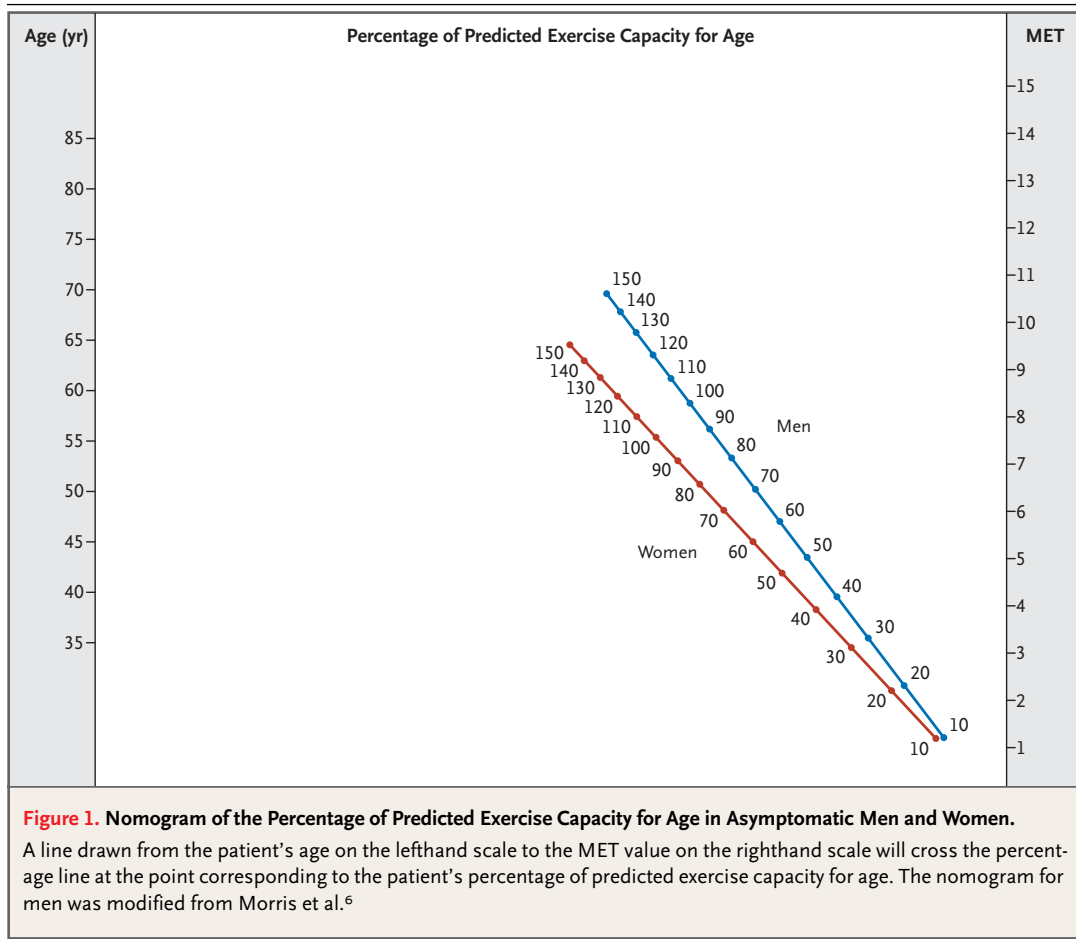
The nomogram for the entire asymptomatic population (the first equation) is shown in Figure 1, with the previously reported nomogram for asymptomatic men provided for comparison.⁶

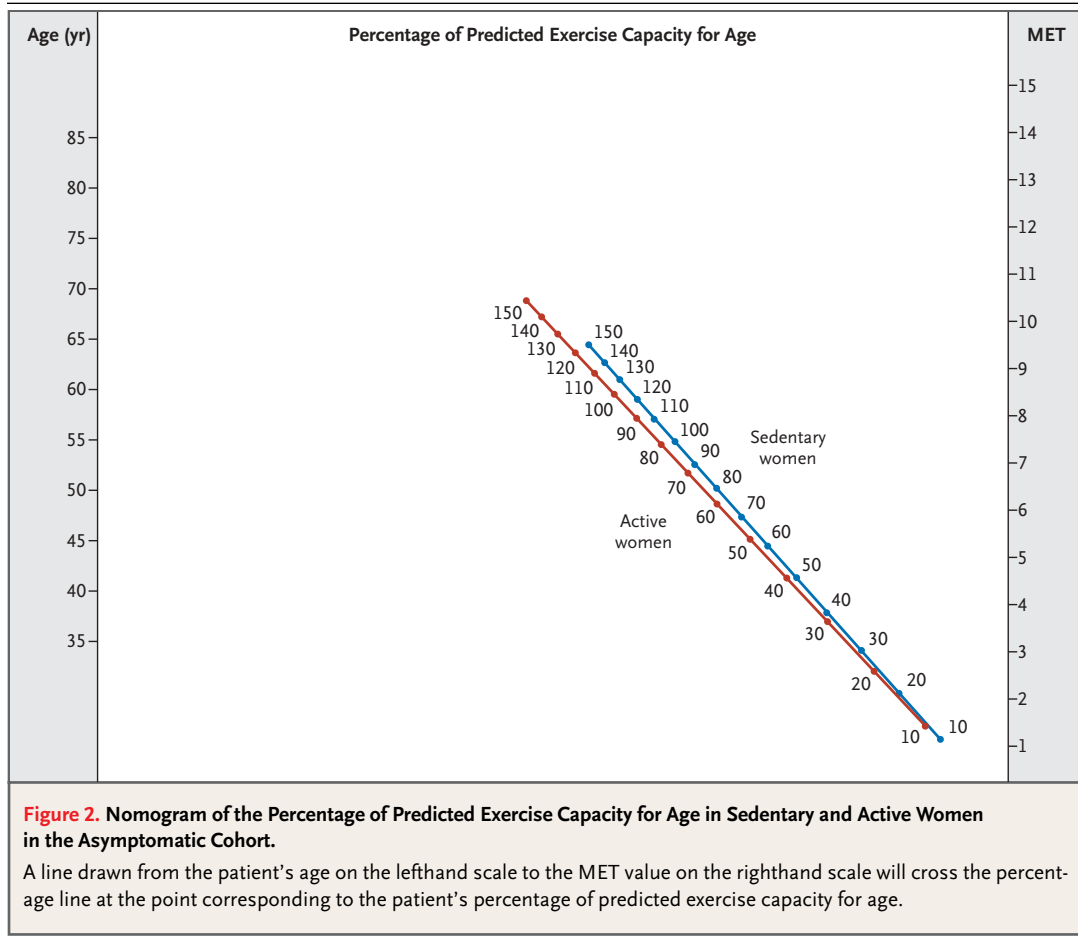
The nomograms based on self-reported activity level (from the second and third equations) are shown in Figure 2. The active women had a greater predicted exercise capacity for any given age than their more sedentary counterparts.

Using the first regression equation to predict normal exercise capacity for age and the equation for the percentage of predicted exercise capacity achieved for age, we determined the percentage of predicted exercise capacity achieved for each participant in both populations. The results ranged from 20 percent to 150 percent of the predicted value for age.

EXERCISE CAPACITY AND PROGNOSIS

In the asymptomatic cohort, there were 180 deaths overall (3 percent) and 58 deaths from cardiac causes (1 percent) during a mean follow-up of 8.4 years (Table 1). Women in this cohort were assumed to be alive if they were not identified as having died by





a search of the National Death Index. In the symptomatic cohort, there were 537 deaths overall (12 percent) and 45 deaths from cardiac causes (1 percent) during a mean follow-up of 5.3 years (Table 1); 3 percent of this cohort was lost to follow-up.

In the asymptomatic cohort, the women whose exercise capacity was less than 85 percent of the age-predicted value had a hazard ratio for death from any cause of 2.03 ($P < 0.001$) and a hazard ratio for death from cardiac causes of 2.44 ($P < 0.001$), as compared with the women whose exercise capacity was at least 85 percent of the age-predicted value (Table 2). In the asymptomatic cohort, as compared with women whose exercise capacity exceeded the age-predicted value by more than 3 MET, women whose exercise capacity was less than that predicted for age (for whom the observed exercise capacity minus the predicted exercise capacity was less than 0 MET) had a hazard ratio for death from any cause of 2.63 ($P = 0.005$) and for death from cardiac causes of 4.27 ($P = 0.045$) (Table 2). The

amount of deviation from one's age-predicted exercise capacity was correlated with the risk of both death from any cause and death from cardiac causes.

In the symptomatic population, as compared with the women whose exercise capacity was at least 85 percent of the age-predicted value, women whose exercise capacity was less than 85 percent of the age-predicted value had a hazard ratio for death from any cause of 2.37 ($P < 0.001$) and for death from cardiac causes of 2.02 ($P < 0.001$) (Table 2). As compared with women whose exercise capacity exceeded the age-predicted value by more than 3 MET, women whose exercise capacity was less than that predicted for age (i.e., a deviation of less than 0 MET) had a hazard ratio for death from any cause of 3.28 ($P < 0.001$) and for death from cardiac causes of 3.80 ($P < 0.001$) (Table 2). The relationship between exercise capacity and the risk of death from cardiac causes was remarkably similar for all age groups in the symptomatic cohort, with two

Table 2. Hazard Ratios for Death from Any Cause and from Cardiac Causes among Women, According to the Deviation from the Expected Exercise Capacity for Age.

Exercise Capacity	Death from Any Cause		Death from Cardiac Causes	
	Asymptomatic Women	Symptomatic Women	Asymptomatic Women	Symptomatic Women
	<i>hazard ratio (95 percent confidence interval)</i>			
Exercise capacity <85% of predicted value for age*	2.03 (1.51–2.71)	2.37 (1.90–2.97)	2.44 (1.46–4.09)	2.02 (1.43–2.85)
Observed exercise capacity minus predicted exercise capacity				
>3 MET†	1.0	1.0	1.0	1.0
0–3 MET	1.70 (0.84–3.44)	1.89 (1.44–2.48)	2.02 (0.46–8.82)	2.21 (1.31–3.27)
<0 MET	2.63 (1.33–5.19)	3.28 (2.47–4.35)	4.27 (1.03–17.6)	3.80 (2.26–6.38)

* The reference group is women whose exercise capacity was at least 85 percent of that predicted for age.

† This group served as the reference group.

exceptions. Young women (less than 55 years of age) with a poor exercise capacity (for whom the observed exercise capacity minus the predicted exercise capacity was less than –2 MET) had an especially high mortality rate, as did the oldest women (older than 70 years) for whom the observed exercise capacity minus the predicted exercise capacity was less than 1 MET (Fig. 3).

USE OF THE NOMOGRAM

Use of the nomogram for the percentage of predicted exercise capacity for age (Fig. 1) requires only the woman's age and exercise capacity achieved (in MET) on the exercise stress test. Drawing a straight line between the age and exercise capacity will allow the determination of the percentage of predicted exercise capacity for age; a value of 100 percent is the mean for any given age. Any result greater than 100 percent indicates better-than-average performance. Any result lower than 100 percent indicates some degree of functional impairment for age. For example, a 60-year-old woman whose exercise capacity was 7 MET on a Bruce-protocol exercise test would have achieved 100 percent of the predicted exercise capacity for her age. In contrast, a 35-year-old woman whose exercise capacity was also 7 MET would have achieved 69 percent of her age-predicted exercise capacity.

DISCUSSION

The first goal of this study was to define the mean age-predicted exercise capacity for women, as depicted by the nomogram in Figure 1. Although such

a nomogram has been established for men and is routinely used in clinical practice, no such nomogram has been established for women, nor have the previous findings in men been validated in the female population.

A number of regression equations for predicting exercise capacity in a variety of male populations have been described.^{6,7,9-11} Three of these studies examined the relationship of exercise capacity to age in healthy men.^{6,7,9} For the asymptomatic women in our study, the regression equation for predicting exercise capacity for age was similar to the regression equations established for healthy men.^{6,7,9} In particular, it was very similar to the equation derived from the 244 healthy men in the study by Morris et al.⁹: predicted MET = 14.7 – (0.11 × age), with an age-adjusted SD of 2.5 ($r = -0.53$, $P < 0.001$). Both equations for asymptomatic men and women share the same constant in the regression equation, and the coefficient differs by only 0.02. Although this number appears small at first glance, the coefficient is multiplied by age. This means that the difference in the predicted exercise capacity for age between men and women will increase as age increases. The nomograms for men and women, when shown side by side, clearly demonstrate the difference between the sexes (Fig. 1).

Within our cohort of asymptomatic women, the regression equation differed on the basis of self-reported physical-activity status. Women were classified as either sedentary or active, on the basis of one question regarding their participation in a regular activity program. Although the validity of this

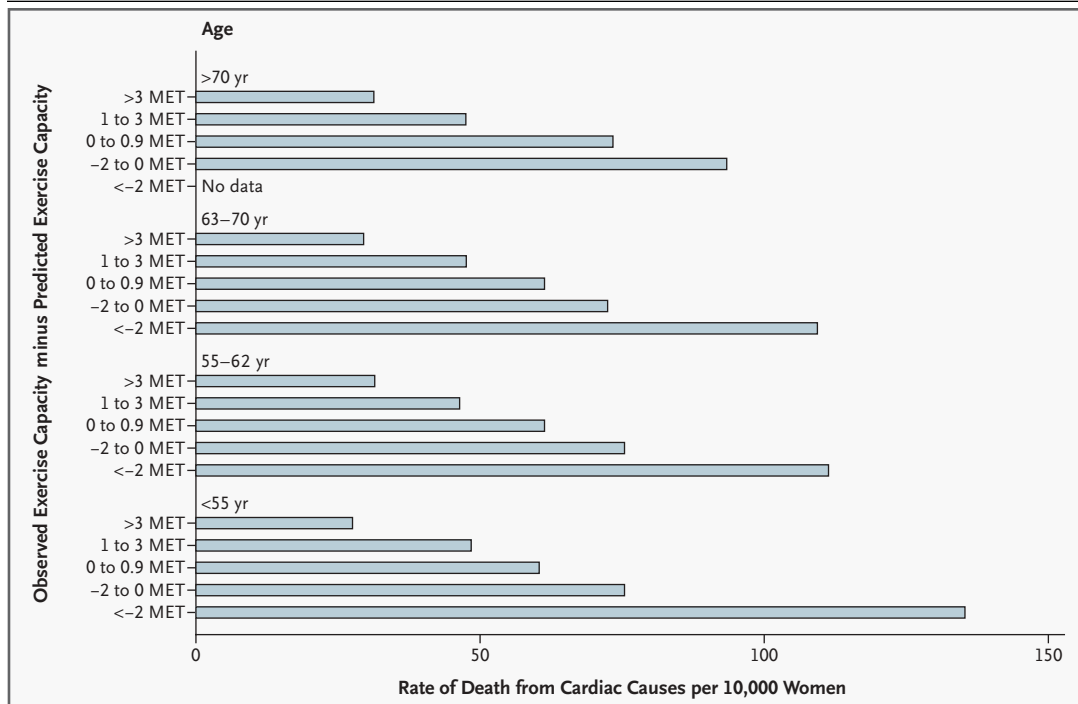


Figure 3. Rate of Death from Cardiac Causes as a Function of the Deviation from the Expected Exercise Capacity for Age among Symptomatic Women.

The rate of death from cardiac causes was stratified according to the difference between the observed and predicted exercise capacity (in MET) in the various age groups.

question has not been established, we have shown a difference in achieved exercise capacity for any age group on the basis of activity status; the more physically active women had a greater exercise capacity at all ages.

The nomogram developed in the cohort of asymptomatic women was also used to determine the percentage of predicted exercise capacity in a referral cohort of racially diverse women from six institutions. Deviation from the established normal values was a significant predictor of the risk of death from any cause and from cardiac causes in both the symptomatic and asymptomatic groups. The further the deviation below the predicted normative value, the greater the risk of death.

The use of the women's nomogram results in a more accurate assessment of prognosis among the women than does the use of the men's nomogram in this group. The sensitivity and specificity of our survival model for predicting the risk of death from any cause among the asymptomatic women are 70 percent and 47 percent, respectively, when the women's nomogram is used. In contrast, the sensitivity

and specificity are 55 percent and 64 percent, respectively, when the men's nomogram is used. Use of the men's nomogram in our cohort would have resulted in 800 more false positive results as compared with the 30 fewer false negative results.

The chief limitation of our study is that the nomogram was created from data on a volunteer cohort of asymptomatic, mostly white women. The referral population differed from the asymptomatic cohort. Traditional cardiac risk factors were expected to be more prevalent in the symptomatic population than in the asymptomatic population, and indeed, these women were older and were more likely to have hypertension and diabetes. The symptomatic women were also more racially diverse, with a stronger representation of black women. Prior studies have suggested that clinicians should use a nomogram for the particular population from which it was created. However, the nomogram we have developed was predictive of the risk of death in the symptomatic group, with hazard ratios similar to those in the asymptomatic group from which it was derived. Whether another nomogram derived

from a symptomatic cohort or from a population with more black women would be a better predictor of the risk of death in our referral cohort is open to question. Such an approach could, however, imply the need for a different nomogram for every clinical population tested, an approach that is not likely to be practical and that might in any case result in findings not very different from ours.

We estimated exercise capacity on the basis of the speed and degree of incline of the treadmill. In contrast, in the study by Morris et al., ventilatory gas exchange was measured directly in asymptomatic men during the stress test.⁶ This distinction is important, since determination of MET levels from a stress test has been demonstrated to overestimate the exercise capacity.¹⁷⁻¹⁹ If oxygen consumption had been measured directly in our study population, the nomograms for men and women would presumably have differed even more.

Despite extensive research on the role of exercise stress testing and exercise capacity, there has been a paucity of data on women, particularly asymptomatic women. Thus, what is normal or ex-

pected for healthy women has not been well established. We have developed a nomogram for women that can be used to predict a woman's expected exercise capacity at any given age and have demonstrated that the resulting measure is a predictor of the risk of death in both asymptomatic and symptomatic cohorts.

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Drs. Gulati and Thisted have a patent pending for the nomogram described in this article. The rights to this patent are owned by Rush University Medical Center and the University of Chicago. Dr. Arnsdorf reports being paid for his role as co-editor-in-chief (cardiovascular medicine) at UpToDate. Dr. Merz reports having received consulting fees from Pfizer, Bayer, Fujisawa, and Merck; lecture fees from Pfizer, AM Medica Communications, Merck, and KOS Pharmaceuticals; and medical-education grants from Pfizer, Wyeth, Procter & Gamble, Novartis, AstraZeneca, and Bristol-Myers Squibb and owning stock in Boston Scientific, IVAX, Lilly, Medtronic, Johnson & Johnson, SCIPIE Insurance, ATS Medical, and Biosite.

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