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## Cardiorespiratory Fitness and Risk of Nonfatal Cardiovascular Disease in Women and Men With Hypertension

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### Abstract

**Background**—Whether the cardioprotective characteristic of higher cardiorespiratory fitness (CRF) extends to adults with manifest hypertension (HTN) is poorly understood.

**Methods**—We examined the association between CRF and nonfatal cardiovascular disease (CVD) events in 8147 men and 1268 women, who, at baseline, were free of known CVD and had HTN based on a history of physician diagnosis or a measured resting blood pressure (BP)  $\geq 140/90$  mm Hg. The CVD events (myocardial infarction, stroke, coronary revascularization) were ascertained from mail-back surveys. The CRF was quantified as maximal treadmill exercise test duration and was grouped for analysis as low (lowest 20% of exercise duration), moderate (middle 40%), and high (upper 40%).

**Results**—A total of 71 CVD events occurred during 12,224 woman-years, and 837 CVD events occurred during 82,366 man-years of follow-up. Age and examination year adjusted CVD rates per 1000 person-years according to low, moderate, and high CRF groups were 10.8, 8.4, and 3.8 (trend  $P = .001$ ) in women, and were 15.3, 10.9, and 7.2 (trend  $P < .001$ ) in men. After further controlling for CVD risk factors, abnormal exercise electrocardiogram (ECG) responses, and family history of CVD, hazards ratios (95% CI) for CVD events across incremental CRF categories were 1.00 (referent), 0.88 (0.74 to 1.06), 0.70 (0.57 to 0.86), trend  $P < .001$ , in men, and were 1.00 (referent), 0.87 (0.48 to 1.58), 0.41 (0.20 to 0.84), trend  $P = .01$ , in women.

**Conclusions**—In adults with HTN, higher CRF is associated with lower risk of nonfatal CVD events, independent of other clinical risk predictors. *Am J Hypertens* 2007;20:608 - 615

### Keywords

Physical fitness; hypertension; cardiovascular diseases; morbidity

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Hypertension (HTN) is a prevalent major modifiable cardiovascular disease (CVD) risk factor among US adults.<sup>1,2</sup> Nearly 1 in 3 or approximately 65 million US adults have HTN. From 1993 to 2003, the age-adjusted death rate from HTN increased about 30%, and the actual number of HTN-associated deaths rose 56%.<sup>1</sup> The estimated total cost of HTN for 2006 exceeds \$60 billion.<sup>1,2</sup> Clearly, HTN is a major economic and public health burden.

Physical activity and cardiorespiratory fitness (CRF) levels are inversely associated with CVD morbidity and mortality.<sup>3,4</sup> Higher physical activity and CRF also are associated with lower risk of new onset HTN.<sup>4-8</sup> Moreover, accumulating evidence shows that exercise

training can lower blood pressure (BP) in hypertensive adults.<sup>9-10</sup> A few epidemiologic studies have reported protective associations between physical activity or CRF and CVD mortality in adults with HTN.<sup>11-14</sup> To our knowledge, the relationship between CRF and nonfatal CVD events in adults with HTN has not been reported. Thus, we examined this issue in a cohort of adults with diagnosed HTN who are enrolled in the Aerobics Center Longitudinal Study (ACLS).

## Methods

### Study Population

Participants were 8147 men and 1268 women, aged 18 to 84 years, who completed a baseline clinical examination between 1971 and 2002 at the Cooper Clinic, Dallas, TX. The current analysis included participants who, at baseline, were free of known CVD, had normal resting electrocardiograms (ECG), and were able to complete an exercise stress test to at least 85% of their age-predicted maximal heart rate. All participants had HTN based on a history of physician diagnosis or a measured resting systolic or diastolic BP of  $\geq 140$  or  $\geq 90$  mm Hg, respectively. All participants responded to at least one follow-up mail-back health survey between 1982 and 2004. The majority of participants was white and from middle and upper socioeconomic strata. Written informed consent was obtained from participants before enrollment into the follow-up study, and the study was reviewed and approved annually by the Cooper Institute Institutional Review Board.

### Clinical Examination

The baseline physician examination and clinical assessment were conducted after an overnight fast of at least 12 h.<sup>6-7</sup> Body mass index (BMI,  $\text{kg}/\text{m}^2$ ) was computed from measured height and weight. After a brief period of sitting quietly, resting BP was measured in the seated position using auscultatory methods with a mercury sphygmomanometer. Systolic and diastolic pressure was recorded as the first and fifth Korotkoff sounds. Serum samples were analyzed for lipids and glucose using standardized bioassays. The presence of diabetes and dyslipidemia was based on a history of physician diagnosis or measured phenotypes that met clinical thresholds for each condition. Smoking habits and alcohol intake were obtained from a questionnaire. Drinks per week of alcohol intake were computed with one drink standardized to 12 ounces of beer, 5 ounces of wine, or 1.5 ounces of hard liquor.

The CRF was quantified as the duration of a maximal treadmill exercise test using a modified Balke-Ware protocol.<sup>6-15</sup> Exercise duration on this protocol is highly correlated with measured maximal oxygen uptake ( $r > 0.90$ ).<sup>6</sup> The percentage of age-predicted maximal heart rate (eg,  $220 - \text{age}$ ) that was achieved during exercise testing was  $101\% \pm 8\%$  in men and was  $100\% \pm 9\%$  in women. To standardize exercise performance, we estimated maximal metabolic equivalents (METs, 1 MET = 3.5 mL of  $\text{O}_2$  uptake/kg/min) from the final treadmill speed and grade.<sup>16</sup> In previous ACLS reports, which have shown low CRF is an independent predictor of mortality and incident nonfatal disease,<sup>7-17</sup> we have defined low, moderate, and high CRF exposures according to the lowest 20%, the middle, and the upper 40%, respectively, of the age- and sex-specific distribution of maximal exercise duration in the overall ACLS population (Table 1). To maintain consistency in our study methods and because a widely accepted clinical categorization of CRF does not exist, we used this approach. Abnormal exercise ECG responses were defined broadly and included rhythm and conduction disturbances and ischemic ST-T wave abnormalities, as described elsewhere.<sup>18</sup> We have found 90% agreement between the ECG interpretation recorded in our database and that of a group of three physicians who read a random sample of 357 patient records.<sup>18</sup>

## Assessment of Outcomes

The CVD events were ascertained from responses to mail-back health surveys. In the overall ACLS population, the aggregate survey response rate is 65% to 75% across seven survey periods. Nonresponse bias is a concern in epidemiologic surveillance and this issue has been investigated in the ACLS.<sup>19</sup> Baseline health histories and clinical measures were similar between responders and nonresponders and between early and late survey responders.<sup>19</sup> Total mortality rates also have been similar between survey responders and nonresponders (unpublished data). Overall, our surveillance experience appears comparable to that described in other long-term cohort studies.<sup>20</sup> Nonfatal CVD end points were obtained using case-finding questions for a physician diagnosis of myocardial infarction (MI) or stroke, and for having a coronary revascularization procedure (coronary artery bypass graft or percutaneous coronary intervention). Participants were asked whether a physician had ever told them that they had a heart attack or stroke, or if they had undergone any coronary interventions. If yes, participants were asked to report the year of the diagnosis or procedure. Our method of ascertaining study end points and the case-finding questions are similar to those used in other established epidemiologic studies on CVD.<sup>21,22</sup> In participants reporting multiple events, the first event was used for analysis. The primary outcome was total CVD events (MI, coronary revascularization, and stroke). We also examined coronary heart disease (CHD) events (MI, coronary revascularization) as a separate end point. In a random sample of these end points ( $n = 50$  each), we applied standard definitions for documenting MI, revascularization, and stroke.<sup>23,24</sup> The percentage of agreement between reported events and medical record review was 88%, 100%, and 89% for MI, revascularization procedures, and stroke, respectively.

## Statistical Analysis

Baseline characteristics of the population were estimated by fitness category and by CVD status for men and women. Trends in covariates by fitness were estimated using F tests. Follow-up time among noncases was calculated as the difference between the date of the baseline examination and the date of the last returned survey where the participant was reported to be free of CVD. Follow-up time among cases was computed as the difference between the baseline examination date and the reported date of the CVD event. If a diagnosis date was not provided, we used the midpoint between the date of the case-finding survey and either the baseline examination date or the date of the last returned survey where the participant was reported to be free of CVD. The mean  $\pm$  SD follow-up interval in years was  $10.1 \pm 7.7$  for men and  $9.6 \pm 7.1$  for women. Cox regression analysis was used to estimate hazards ratios and 95% confidence intervals of CVD events according to exposure categories. The proportional hazards assumption was examined by comparing the cumulative hazards plots grouped on exposure in women and in men; no appreciable violations were noted. We constructed an indicator variable to account for differences in survey response frequency. All multivariable analyses included as covariables: age (years), examination year, survey response frequency, smoking status (current smoker or not), alcohol intake ( $\geq 5$  drinks/week or not), abnormal exercise ECG responses (present or not), and family history of CVD (present or not). We conducted an additional analysis that further adjusted for differences in the following five factors that may be intermediate in the causal pathway between CRF and CVD: resting systolic and diastolic BP (per mm Hg), diabetes and dyslipidemia (present or not for each), and BMI (per  $\text{kg}/\text{m}^2$ ). Tests of linear trends were computed using ordinal scoring. There were no a priori hypotheses on sex differences in CVD event rates or in the association between CRF and CVD risk. All  $P$  values are two-sided and  $P < .05$  was regarded as statistically significant.

## Results

There were 837 CVD events (288 MI, 183 strokes, 366 revascularizations) during 82,366 man-years of exposure and 71 CVD events (28 MI, 30 strokes, 13 revascularizations) during 12,224 woman-years of exposure. At baseline, low fit individuals (Table 2) were slightly younger than those in the moderate and high fitness categories and CVD risk factors were often less favorable. Compared with noncases, individuals who developed CVD were older, had lower CRF, and had higher prevalence of major CVD risk factors (Table 3).

Rates and hazards ratios of CVD events according to CRF groups among men are shown in Table 4. An inverse gradient of total CVD event rates was observed across incremental CRF groups (trend  $P < .001$ ). After adjusting for covariables, men with moderate and high CRF had a 14% and 34% lower risk of CVD events than men with low CRF (trend  $P < .001$ ). The inverse association between CRF and CVD events remained significant after additional adjustment for BMI, resting BP, diabetes, and dyslipidemia (trend  $P < .001$ ). Similar inverse patterns of association were observed between CRF and CHD events ( $P < .001$ ).

In women (Table 4), rates of total CVD events were inversely associated with CRF (trend  $P = .001$ ). After adjustment for covariables, women with moderate and high CRF had a 6% and 51% lower risk of CVD events than women with low CRF (trend  $P = .03$ ). The CRF remained inversely associated with CVD risk after additional adjustment for intermediate risk factors (trend  $P = .01$ ). The CRF also was inversely associated with rates of CHD events (trend  $P = .004$ ); however, the significant inverse trend was attenuated by adjustment for covariables ( $P = .08$ ) and for intermediate risk factors ( $P = .09$ ).

We next examined whether the severity of baseline HTN modified the association between CRF and CVD incidence (Figs. 1 and 2). For this analysis, measured BPs and reported HTN status at baseline were used to group participants into the following categories: 2 controlled HTN (BP  $< 140/90$  mm Hg with history of physician-diagnosed HTN), stage 1 HTN (BP  $140/90$  to  $160/100$  mm Hg, with or without physician diagnosis), or stage 2 HTN (BP  $\geq 160/100$  mm Hg, with or without physician diagnosis). There was weak statistical evidence of interaction between CRF and HTN severity in predicting CVD events in men ( $\chi^2_{df=1} = 3.4$ ,  $P = .06$ ) and in women ( $\chi^2_{df=1} = 2.4$ ,  $P = .12$ ), although statistical power to examine interaction effects likely was inadequate. In men, a significant inverse gradient of age and examination year-adjusted CVD rates were seen across incremental CRF levels within each HTN group. Across HTN strata, men in the lowest CRF group had a 1.6- to 2.6-fold higher rate of total CVD events than men in the highest CRF group. In women, CRF was inversely associated with CVD rates within HTN groups; however, the rate differences were not statistically significant.

## Discussion

The CRF is inversely associated with the risk of all-cause and CVD mortality in initially asymptomatic women and men.<sup>3,4</sup> Exposure to cardiovascular risk factors has been variable in these cohorts. Therefore, statistical power often is insufficient to examine the association between CRF and CVD within population groups that have higher CVD rates because of the presence of clinically manifest disease, such as HTN. In a previous ACLS report, CVD death rates of 26.7, 14.2, and 11.9 per 10,000 man-years were seen across low, moderate, and high CRF groups (trend  $P = .02$ ), respectively, in hypertensive men.<sup>12</sup> Inverse patterns of association between physical activity or CRF exposures and CVD mortality generally have been reported in the few other published studies in hypertensive adults.<sup>11,13,14</sup> This suggests that physical activity and CRF may favorably influence the etiologic pathway between HTN and fatal clinical CVD events. The risk of CVD mortality may be different

from that associated with having a nonfatal event.<sup>25</sup> To more thoroughly evaluate the role of physical activity or CRF in primary CVD prevention, it is important to examine relationships with nonfatal CVD events and not merely with mortality.

The present study demonstrated that higher CRF was associated with significantly lower rates of nonfatal CVD events in adults with clinically documented HTN. The inverse association between CRF and CVD events was present in women and in men and persisted after considering the potential confounding effects of other established CVD risk predictors. The severity of baseline HTN did not modify the inverse pattern of association between CRF and CVD. Protective associations also were seen between CRF and nonfatal CHD. Some of the inverse trends in women were attenuated in multivariable analyses due to low statistical power. This is one of the largest prospective studies, and to our knowledge the first in women, to relate an objectively measured CRF exposure with the occurrence of nonfatal CVD in a population sample of adults with HTN.

The Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure guidelines include both pharmacologic and lifestyle interventions for primary HTN prevention and for managing the risk of HTN-related morbidity and mortality.<sup>2</sup> Although promoting higher physical activity levels is mentioned with diet and stress management as components of antihypertensive lifestyle modification, historically the major hygienic focus has been on diet modification. The CRF is an objective physiologic measure that reflects the functional effects of physical activity habits, genetics, and diseases status.<sup>26</sup> Previous ACLS investigations have shown favorable associations between CRF and BP-related health issues. The CRF is inversely associated with the prevalence of elevated clinical BP,<sup>27</sup> the incidence of HTN,<sup>6,7</sup> and with the rates of total and CVD mortality in men with diagnosed HTN.<sup>12,28</sup> The present results extend these previous findings to nonfatal CVD end points in women and men with documented HTN.

The cardioprotection of higher CRF was observed across a broad range of elevated BPs. In men with stage 2 HTN, CVD incidence rates in moderately and highly fit men were 17% and 35% lower, respectively, than those in low fit men; similarly, lower event rates of 29% to 41% and 57% to 65% were seen in moderately and highly fit men, respectively, with controlled HTN and with stage 1 HTN. Women with moderate and high CRF experienced CVD rates that were 14% to 75% lower than those in women with low CRF who had controlled, stage 1, or stage 2 HTN. Statistical power of these group analyses in women, however, was limited by a small number of events. Comparatively, clinical trial data indicate that antihypertensive drug therapy is associated with an average CVD risk reduction of 20-40%.<sup>2</sup> Thus, based on observational findings from the present study and other studies,<sup>11-14</sup> higher levels of physical activity and CRF may confer similar CVD risk reduction in hypertensive adults, as is seen with antihypertensive drug therapy. The cardiovascular benefits in hypertensive adults may be even greater in response to a combined pharmacologic and physical activity intervention. Data from randomized controlled trials on the independent and joint effect of drug therapy and exercise training on CVD events in hypertensive patients would strengthen these suggestive observational findings. The findings reported here and elsewhere<sup>11-14</sup> reinforce national recommendations<sup>29</sup> and underscore the importance of promoting higher CRF levels, presumably through greater physical activity, for primary CVD prevention in high-risk population groups, such as individuals with HTN.

The current study has strengths and limitations that should be considered. One of the strengths of the study is the extensive baseline examination. Undetected subclinical disease at baseline is a concern in prospective studies. It is less likely in our cohort because of the comprehensive physician examination and objective measurements completed by participants. Other strengths include the large sample of women and men with a clinically

documented HTN, the use of maximal exercise testing to quantify CRF, the large number of person-years of follow-up, and a generally adequate number of events for sex-specific analyses. The CRF was associated with CVD events independent of other risk factors, which strengthens causal inferences. Biological plausibility for the observed associations may be through enhanced endothelial cell function and coronary flow reserve, reduced myocardial oxygen demand under a variety of circumstances, higher myocardial arrhythmia threshold, improved endogenous thrombolytic activity, and lower levels of circulating atherothrombotic cytokines, which promote a more stable coronary plaque milieu.<sup>4</sup>

The homogeneity of the ACLS population on sociodemographic factors deserves comment. On one hand this enhances the internal validity of our findings by reducing the degree of confounding by these factors. On the other hand, our findings may not apply to individuals who are not white or who are from lower socioeconomic strata. We are not aware of biological reasons that the association between CRF and CVD would be greatly different across race-ethnicity or sociodemographics. Care should be taken if attempting to generalize these results to other populations.

We did not have sufficient information on medication usage, menopausal status, or dietary habits to include in our analysis. It is possible that residual confounding by these factors may exist, although it seems unlikely that it would account for all of the observed association between fitness and CVD risk. Due to the widespread geographic distribution of patients evaluated at the Cooper Clinic, we were unable to verify all reported CVD events. However, based on a random sample of verified events, it appears that an acceptable level of agreement exists between the participants' self-reported histories and their medical records. The present study related a single baseline CRF exposure with the 10-year occurrence of primary CVD events. Changes during the follow-up period in CRF or other risk-reducing behaviors, in the awareness and treatment of HTN, and in the clinical definition of HTN may, in part, explain the pattern of CVD event rates seen across exposure categories. Changes in CRF status and other health-related behaviors likely would result in nondifferential misclassification in a prospective study, which would weaken rather than strengthen the exposure-outcome association. Changes in the clinical definition of HTN, increased awareness, and improved treatment of HTN did occur during the period 1971 to 2004. To account in part for these potential temporal effects, we included in our analyses examination year and a term for survey response pattern. It was not possible to conduct a more extensive examination on the effect that these issues may have had on CVD events during the follow-up interval.

We conclude that CRF is inversely associated with the incidence of nonfatal CVD events in women and men with HTN. The association is graded, biologically plausible, and observed within strata of greater HTN severity. These findings suggest that functional capacity is an important prognostic indicator in hypertensive adults beyond traditional risk factors. The CRF can be enhanced in most individuals, including those with HTN,<sup>30</sup> through participation in physical activities such as brisk walking, cycling, and jogging, for 30 min or more on most days of the week.<sup>29</sup> Given the high population prevalence of HTN and because hypertension control rates still are far below the Healthy People 2010 Goal of 50%, the public health burden attributed to HTN continues to be large and may well increase in coming years. We, therefore, believe that clinicians should consider the potential independent cardioprotective benefits of greater physical activity and CRF, and vigilantly counsel their sedentary hypertensive patients to become more physically active and improve their CRF as a cornerstone of HTN management and primary CVD prevention.

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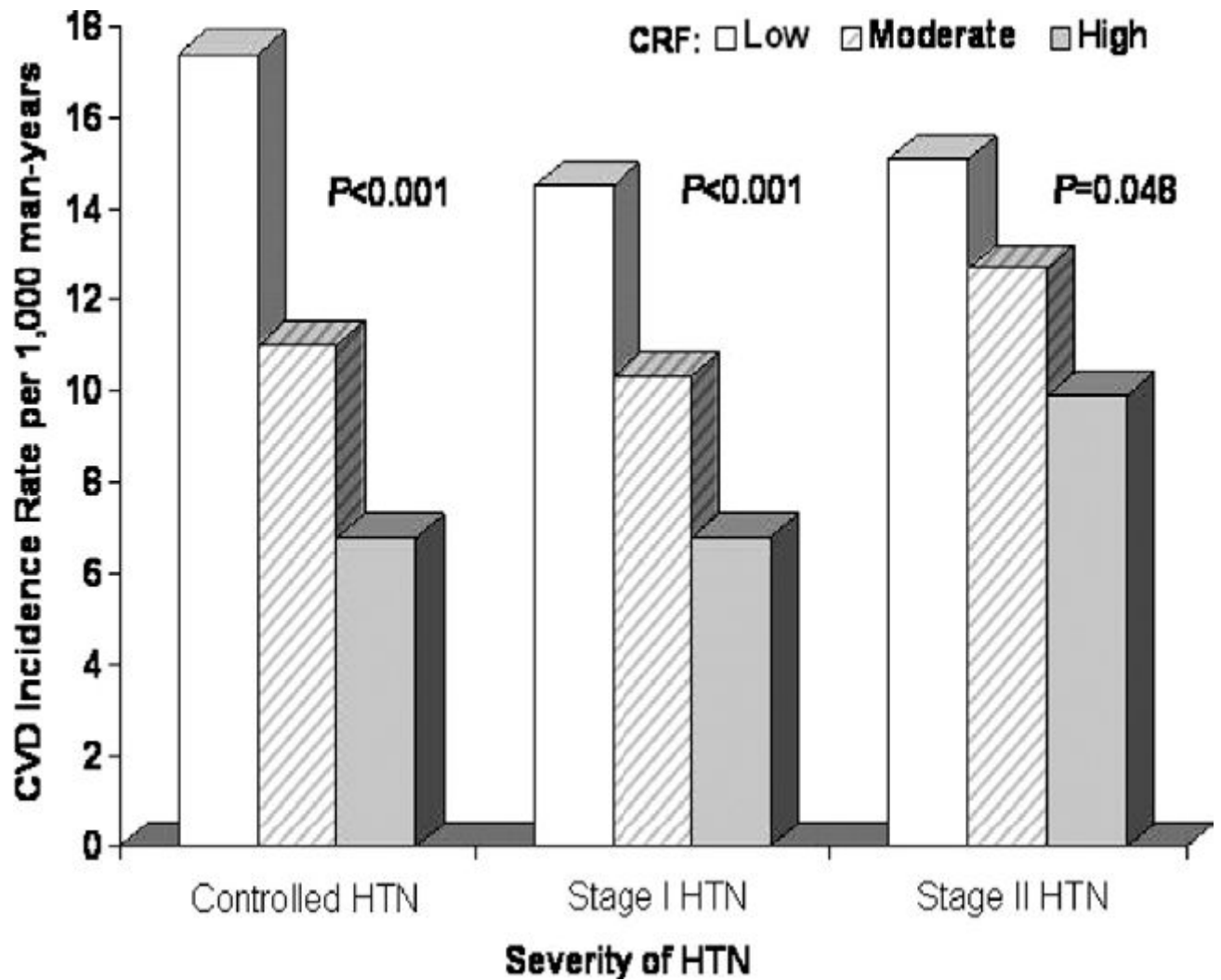
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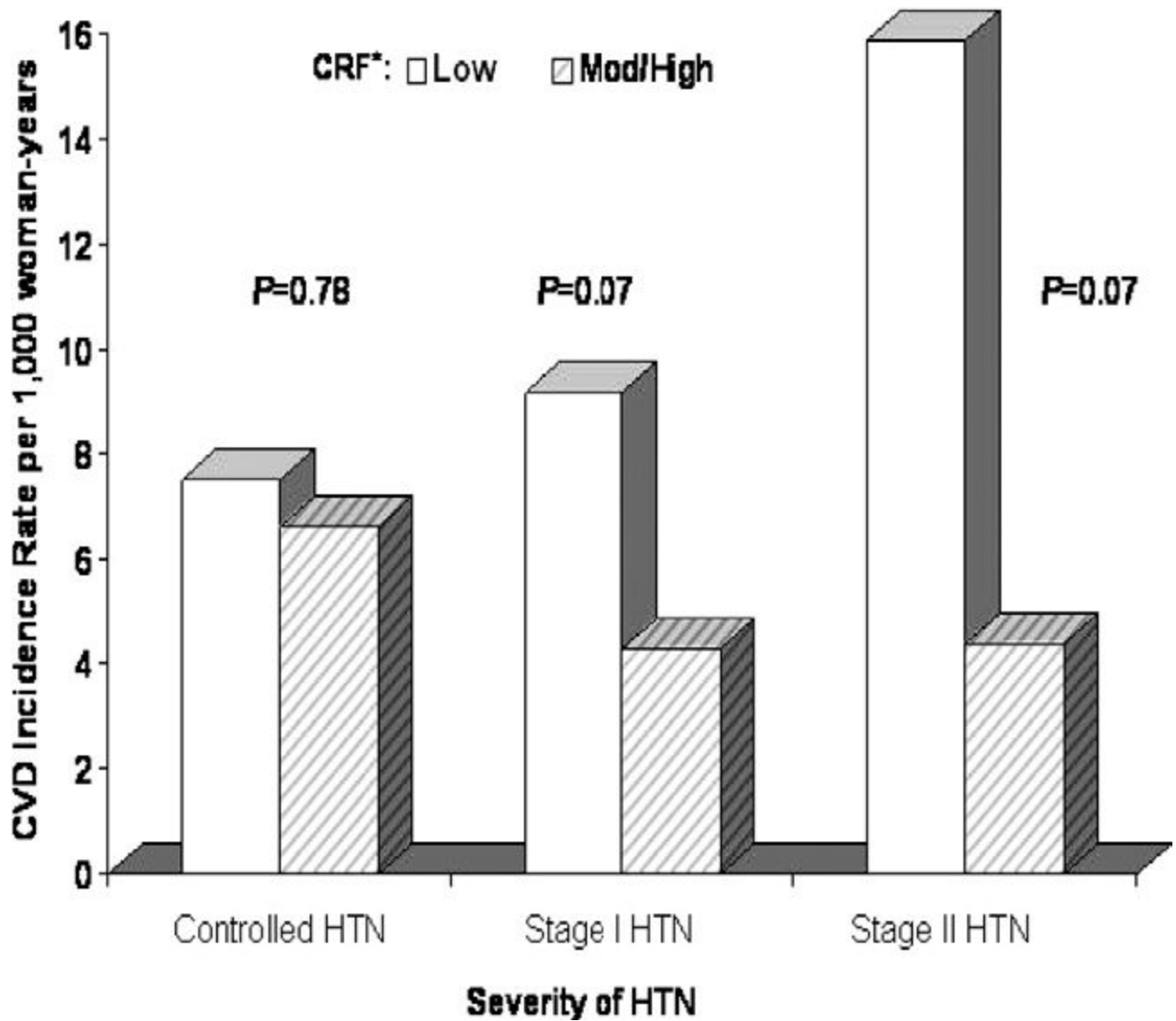
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**FIG. 1.**

Age and examination year adjusted rates of total CVD events (per 1000 man-years) by levels of cardiorespiratory fitness and severity of HTN in 8147 hypertensive men. The number of men (and cases) in the low, moderate, and high CRF groups were 418 (47), 697 (86), and 546 (51) in controlled HTN; were 1027 (111), 1973 (196), and 2172 (184) in stage 1 HTN; and were 410 (47), 533 (68), and 371 (47) in stage 2 HTN. CRF = cardiorespiratory fitness; CVD = cardiovascular disease; HTN = hypertension.



**FIG. 2.**

Age and examination year adjusted rates of total CVD events (per 1000 woman-years) by levels of cardiorespiratory fitness and severity of HTN in 1268 hypertensive women.

\*Moderate and high fitness were collapsed because of the small number of CVD events in these cells. The number of women (and cases) in the low and moderate/high CRF groups were 91 (6) and 317 (22) in controlled HTN; were 109 (9) and 590 (25) in stage 1 HTN; and were 35 (4) and 126 (5) in stage 2 HTN. CRF = cardiorespiratory fitness; CVD = cardiovascular disease; HTN = hypertension.

**Table 1**

Age- and sex-specific maximal treadmill\* exercise duration and estimated MET levels of cardiorespiratory fitness

Age (y)	CRF group	Men		Women	
		Duration (min)	METs	Duration (min)	METs
20-39	Low	<15.0	<10.4	<10.3	<8.2
	Moderate	15.0-20.3	10.4-13.1	10.3-15.0	8.2-10.4
	High	>20.3	>13.1	>15.0	>10.4
40-49	Low	<13.5	<9.9	<8.9	<7.6
	Moderate	13.5-19.0	9.9-12.2	8.9-13.0	7.6-9.4
	High	>19.0	>12.2	>13.0	>9.4
50-59	Low	<11.0	<8.5	<7.0	<6.7
	Moderate	11.0-16.0	8.5-10.8	7.0-10.7	6.7-8.5
	High	>16.0	>10.8	>10.7	>8.5
≥60	Low	<7.8	<7.2	<5.5	<5.8
	Moderate	7.8-13.1	7.2-9.5	5.5-9.0	5.8-7.6
	High	>13.1	>9.5	>9.0	>7.6

CRF = cardiorespiratory fitness; METs = metabolic equivalents.

\* Treadmill exercise testing was performed using a modified Balke-Ware protocol as described in the Methods section.

Table 2

Baseline characteristics of study participants by CRF category among men and women

	Men				P for trend
	Total (n = 8147)	Low CRF (n = 1855)	Moderate CRF (n = 3203)	High CRF (n = 3089)	
Age (mean ± SD, y)	47.4 ± 9.8	45.0 ± 9.5	47.4 ± 9.7	49.0 ± 9.7	<.001
Body mass index (mean ± SD, kg/m <sup>2</sup> )	27.1 ± 4.0	29.9 ± 5.1	27.2 ± 3.3	25.4 ± 2.7	<.001
Blood pressure (mean ± SD, mm Hg)					
Systolic	133 ± 14	134 ± 14	133 ± 14	133 ± 14	<.001
Diastolic	90 ± 9	91 ± 9	90 ± 9	89 ± 8	<.001
Current smoker, no. (%)	1357 (16.7)	536 (28.9)	558 (17.4)	263 (8.5)	<.001
Alcohol intake (≥5 drinks per week), no. (%)	3238 (39.7)	807 (43.5)	1314 (41.0)	1117 (36.2)	<.001
Abnormal ECG during exercise, no. (%)	596 (7.3)	184 (9.9)	241 (7.5)	171 (5.5)	<.001
Diabetes mellitus, * no. (%)	677 (8.3)	253 (13.6)	277 (8.7)	147 (4.8)	<.001
Dyslipidemia, † no. (%)	5569 (68.4)	1619 (87.3)	2337 (73.0)	1613 (52.2)	.88
Family history of premature CVD, no. (%)	1346 (16.5)	316 (17.0)	517 (16.1)	513 (16.6)	.70
			Women		
	Total (n = 1268)	Low CRF (n = 235)	Moderate CRF (n = 437)	High CRF (n = 596)	P for trend
Age (mean ± SD, y)	50.3 ± 10.1	47.6 ± 10.4	49.4 ± 10.1	52.0 ± 9.7	<.001
Body mass index (mean ± SD, kg/m <sup>2</sup> )	24.2 ± 4.5	27.3 ± 6.2	24.5 ± 4.2	22.9 ± 3.1	<.001
Blood pressure (mean ± SD, mm Hg)					
Systolic	131 ± 17	130 ± 16	131 ± 17	132 ± 16	.48
Diastolic	87 ± 10	87 ± 11	87 ± 10	88 ± 9	.38
Current smoker, no. (%)	89 (7.0)	31 (13.2)	34 (7.8)	24 (4.0)	<.001
Alcohol intake (≥5 drinks per week), no. (%)	217 (17.1)	46 (19.6)	105 (24.0)	66 (11.1)	<.001
Abnormal ECG during exercise, no. (%)	121 (9.5)	28 (11.9)	44 (10.1)	49 (8.2)	.24
Diabetes mellitus, * no. (%)	71 (5.6)	19 (8.1)	29 (6.6)	23 (3.9)	.03
Dyslipidemia, † no. (%)	605 (47.7)	158 (67.2)	251 (57.4)	196 (32.9)	.67
Family history of premature CVD, no. (%)	260 (20.5)	35 (14.9)	95 (21.7)	130 (21.8)	.06

CRF = cardiorespiratory fitness; CVD = cardiovascular disease; ECG = electrocardiogram; SD = standard deviation.

\* Diabetes mellitus was defined as a fasting plasma glucose concentration ≥7.0 mmol/L (126 mg/dL), a history of physician diagnosis, or insulin use

<sup>f</sup> Dyslipidemia was defined as one or more of the following: total cholesterol  $\geq 6.20$  mmol/L (240 mg/dL) or a history of physician diagnosis, triglycerides  $\geq 2.26$  mmol/L (200 mg/dL), or HDL  $< 1.03$  mmol/L (40 mg/dL).

**Table 3**  
Baseline characteristics of study participants by sex and cardiovascular disease event status

Characteristic	Men		Women	
	Noncase (n = 7310)	Case (n = 837)	Noncase (n = 1197)	Case (n = 71)
Age (mean ± SD, y)	46.9 ± 9.8	52.2 ± 8.5	50.1 ± 10.1	54.0 ± 9.2
Body mass index (mean ± SD, kg/m <sup>2</sup> )	27.2 ± 4.0	26.9 ± 3.6	24.3 ± 4.3	23.8 ± 3.8
Maximal METs (mean ± SD)	11.0 ± 2.4	10.2 ± 2.3	8.8 ± 2.1	7.7 ± 1.7
Blood pressure (mean ± SD, mm Hg)				
Systolic	133 ± 14	135 ± 15	131 ± 17	133 ± 13
Diastolic	90 ± 9	89 ± 9	87 ± 9	87 ± 9
Current smoker, no. (%)	1219 (16.7)	138 (16.5)	82 (6.9)	7 (9.9)
Alcohol intake (≥5 drinks per week), no. (%)	2926 (40.0)	312 (37.3)	199 (16.6)	18 (25.4)
Abnormal ECG during exercise, no. (%)	451 (6.2)	145 (17.3)	106 (8.9)	15 (21.1)
Diabetes mellitus,* no. (%)	571 (7.8)	106 (12.7)	67 (5.6)	4 (5.6)
Dyslipidemia, <sup>†</sup> no. (%)	4912 (67.2)	657 (78.5)	561 (46.9)	44 (62.0)
Family history of premature CVD, no. (%)	1193 (16.3)	153 (18.3)	248 (20.7)	12 (16.9)

CRF = cardiorespiratory fitness; CVD = cardiovascular disease; ECG = electrocardiogram; SD = standard deviation.

\* Diabetes mellitus was defined as a fasting plasma glucose concentration ≥7.0 mmol/L (126 mg/dL), a history of physician diagnosis, or insulin use

<sup>†</sup> Dyslipidemia was defined as one or more of the following: total cholesterol ≥6.20 mmol/L (240 mg/dL) or a history of physician diagnosis, triglycerides ≥2.26 mmol/L (200 mg/dL), or HDL <1.03 mmol/L (40 mg/dL).

**Table 4**  
Rates and hazards ratios for cardiovascular disease events by CRF groups in hypertensive men and women

Outcomes	CRF status	Person-years of follow-up	Events	Rate*	HR <sup>†</sup>	95% CI	HR <sup>‡</sup>	95% CI
<b>Men</b>								
Total CVD								
	Low CRF	16,268	205	15.3	1.00	Referent	1.00	Referent
	Moderate CRF	31,902	350	10.9	0.86	0.72-1.03	0.88	0.74-1.06
	High CRF	33,763	282	7.2	0.66	0.54-0.80	0.70	0.57-0.86
	<i>P</i> linear trend			<.001		<.001		<.001
CHD								
	Low CRF	16,472	180	12.9	1.00	Referent	1.00	Referent
	Moderate CRF	32,222	295	9.1	0.87	0.71-1.05	0.89	0.73-1.08
	High CRF	34,103	232	5.9	0.67	0.54-0.82	0.71	0.57-0.89
	<i>P</i> linear trend			<.001		<.001		.002
<b>Women</b>								
Total CVD								
	Low CRF	2160	29	10.8	1.00	Referent	1.00	Referent
	Moderate CRF	4239	32	8.4	0.94	0.52-1.70	0.87	0.48-1.58
	High CRF	5757	20	3.8	0.49	0.24-0.97	0.41	0.20-0.84
	<i>P</i> linear trend			.001		.03		.01
CHD								
	Low CRF	2193	13	6.5	1.00	Referent	1.00	Referent
	Moderate CRF	4318	21	4.7	0.96	0.46-1.97	0.96	0.46-2.01
	High CRF	5781	12	2.0	0.47	0.20-1.13	0.47	0.19-1.17
	<i>P</i> linear trend			.004		.08		.09

CHD = coronary heart disease; CI = confidence interval; CRF = cardiorespiratory fitness; CVD = cardiovascular disease; HR = hazards ratio.

\* Rate is expressed as per 1000 person-years and adjusted for age and examination year

<sup>†</sup> Adjusted for the above plus survey indicator, current smoking (yes or not), alcohol intake ( $\geq 5$  drinks/wk, or not), family history of CVD (present or not), and abnormal exercise electrocardiogram responses (present or not)

<sup>‡</sup> Adjusted for the above plus body mass index ( $\text{kg}/\text{m}^2$ ), resting systolic and diastolic blood pressure (mm Hg), diabetes, or dyslipidemia (present or not for each).