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A Prospective Study of Muscular Strength and All-Cause Mortality in Men With Hypertension

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- Objectives** This study sought to assess the impact of muscular strength on mortality in men with hypertension.
- Background** Muscular strength is inversely associated with mortality in healthy men, but this association has not been examined in men with hypertension.
- Methods** We followed 1,506 hypertensive men age 40 years and older enrolled in the Aerobics Center Longitudinal Study from 1980 to 2003. Participants received an extensive medical examination at baseline. Muscular strength was quantified by combining 1 repetition maximum (1-RM) measures for leg and bench press and cardiorespiratory fitness assessed by maximum exercise test on a treadmill.
- Results** During an average follow-up of 18.3 years, 183 deaths occurred. Age-adjusted death rates per 10,000 person-years across incremental thirds of muscular strength were 81.8, 65.5, and 52.0 ($p < 0.05$ for linear trend). Multivariable Cox regression hazard ratios were 1.0 (reference), 0.81 (95% confidence interval [CI]: 0.57 to 1.14), and 0.59 (95% CI: 0.40 to 0.86) across incremental thirds of muscular strength. After further adjustment for cardiorespiratory fitness, those participants in the upper third of muscular strength still had a lower risk of death (hazard ratio [HR]: 0.66; 95% CI: 0.45 to 0.98). In the muscular strength and CRF combined analysis, men simultaneously in the upper third of muscular strength and high fitness group had the lowest mortality risk among all combination groups (HR: 0.49; 95% CI: 0.30 to 0.82), with men in the lower third of muscular strength and low fitness group as reference.
- Conclusions** High levels of muscular strength appear to protect hypertensive men against all-cause mortality, and this is in addition to the benefit provided by cardiorespiratory fitness. (J Am Coll Cardiol 2011;57:1831–7) © 2011 by the American College of Cardiology Foundation

Hypertension is associated with an increased risk of all-cause and cardiovascular disease (CVD) mortality (1). Re-

cent calculations show nearly 8 million deaths worldwide (about 13.5% of the global total) attributable to high blood pressure (2). It remains a major public health problem in the United States, with 58.4 million Americans (28.7%) age 18 years or older having hypertension (systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg) (1). Although awareness, treatment, and control of hypertension appear to be improving in recent decades (1), this is still far from optimal, and with the ongoing obesity epidemic, there may be an increase in most CVD, including hypertension (3).

Cardiorespiratory fitness (CRF) provides strong and independent prognostic information about the overall risk of illness and death across a broad spectrum of medical conditions, including hypertension (4–6). It is generally accepted that regular exercise can help prevent the development of hypertension, lower blood pressure in normotensive and hypertensive adults, and reduce mortality risk in individuals with hypertension (7,8). The independent role of

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Abbreviations and Acronyms

CI	= confidence interval
CRF	= cardiorespiratory fitness
CVD	= cardiovascular disease
HR	= hazard ratio
1-RM	= 1 repetition maximum

muscular strength in the prevention of chronic disease is now increasingly being recognized (9). Resistance-type physical activities are major determinants of muscular strength and are currently prescribed by prestigious health organizations for improving health and fitness (8,10). Findings from meta-analyses indicate that resistance training could produce a reduction of approximately 3.0 and 3.5 mm Hg for resting systolic and diastolic blood pressure, respectively (11,12), which represents approximate decreases of 2% and 4%, respectively (12). The blood pressure-lowering effects of resistance training seem to be even more pronounced in individuals with existing hypertension (13,14). Taken together, these results suggest that moderate intensity resistance training is not contraindicated and could become part of the nonpharmacological intervention strategy to prevent and combat high blood pressure (11).

Several prospective studies have shown that muscular strength is inversely associated with all-cause (15–22) and cancer (22,23) mortality, but the association in persons with hypertension has yet to be examined. Any modifiable factor able to decrease the risk of mortality among hypertensive individuals would be of great interest from a public health perspective. We hypothesized that muscular strength would have an independent protective effect on all-cause mortality in hypertensive men.

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Methods

Data for the current report are from the Aerobics Center Longitudinal Study, a prospective study on the association of clinical and lifestyle factors with health outcomes in patients examined at the Cooper Clinic in Dallas, Texas, from 1970. Between 1980 and 1989, 10,265 men underwent muscular strength tests as part of the comprehensive medical examination. Participants came to the clinic for periodic preventive health examinations and for counseling on diet, exercise, and other lifestyle factors associated with an increased risk of chronic disease. Participants, thus, were volunteers, were not paid, and were not recruited to the study as would be the case for a clinical trial. Many were sent by their employers for the examination, some were referred by their physicians, and others were self-referred.

Only participants age 40 years or older and with resting blood pressure $\geq 140/90$ mm Hg or previous physician-diagnosed hypertension were included in the present study ($n = 1,668$). The exclusion of younger participants was due to the low prevalence of hypertension at those ages (1). Among those finally selected, participants were excluded if they reported a history of myocardial infarction, stroke, or cancer ($n = 81$); failed to achieve at least 85% of age-

predicted maximum heart rate during the treadmill test ($n = 77$); or died during the first year of follow-up ($n = 4$). These criteria resulted in 1,506 men, all of them with a body mass index ≥ 18.5 kg/m². Participants were predominantly white and well educated and belonged to middle and upper socioeconomic strata. All participants gave informed consent to participate in the clinical examination and follow-up study. The Cooper Institute Institutional Review Board reviewed and approved the study protocol annually.

Clinical examination. The clinical examination and measures of muscular strength and CRF are described in detail elsewhere (24,25). Briefly, the baseline examination was completed after an overnight fast of at least 12 h and included a physical examination and an array of clinical measurements. Body mass index was computed as weight in kilograms divided by height in meters squared, measured with a standard clinical scale and stadiometer. Resting systolic and diastolic blood pressure was measured in the seated position as the first and fifth Korotkoff sounds, using standard auscultation methods after at least 5 min of sitting quietly (26). Two or more readings separated by 2 min were averaged. If the first 2 readings differed by more than 5 mm Hg, additional readings were obtained and averaged. Concentrations of total cholesterol and glucose were measured using automated techniques in accordance with the standards of the Centers for Disease Control and Prevention lipid standardization program. Hypercholesterolemia was defined as a total cholesterol concentration of ≥ 240 mg/dl. Diabetes mellitus was defined as a fasting plasma glucose concentration of ≥ 126 mg/dl, previous physician diagnosis of diabetes, or use of insulin. Participants completed a questionnaire on medical history that included a personal history of myocardial infarction, stroke, hypertension, diabetes, and cancer; a family history of CVD; a family history of cancer; smoking status; alcohol intake; and physical activity (active or inactive). Physical inactivity was defined as reporting no physical activity during leisure time in the 3 months before the examination.

We assessed muscular strength in the upper and lower body using a standardized strength testing protocol and variable resistance weight machines (Universal Equipment, Cedar Rapids, Iowa) (25). Upper body strength was assessed with a 1 repetition maximum (1-RM) supine bench press, and lower body strength was assessed with a 1-RM seated leg press. Initial loads were 70% of body weight for the bench press and 100% for the leg press. After a brief rest period, we added increments of 2.27 to 4.54 kg until maximum effort was achieved for each lift, usually after ≤ 5 trials. Participants were able to lift the initial load at least 1 time. They were instructed on proper breathing and lifting form for each movement. The intraclass correlation coefficient for 1-RM bench and 1-RM leg press was 0.90 and 0.83, respectively, in a subgroup of 246 men who underwent 2 muscular strength assessments within 1 year (25).

A muscular strength index was computed by taking each individual's 1-RM score for the bench press and leg

press, expressed as weight lifted per kilogram body weight, and dividing the scores into 3 age groups (40 to 49 years, 50 to 59 years, and ≥ 60 years). In each age group, the individual's scores were standardized using the formula: standardized value = (value - mean)/SD. These new scores for the bench press and leg press were averaged to express an age-specific standardized composite score for each individual, following our earlier studies (14,22,23). For the analyses, we used thirds of this age-specific strength score.

We assessed CRF by a maximum treadmill test using a modified Balke protocol (24,27). Participants were encouraged to give maximum effort, and the test was stopped when participants reached volitional exhaustion or the doctor intervened for medical reasons. The mean percentage of age-predicted maximum heart rate ($220 - \text{age}$) achieved during exercise was 102.3 ± 7.1 , indicating that a majority of participants achieved maximum effort. Exercise duration using this protocol is highly correlated with measured maximum oxygen uptake ($r = 0.92$) (28). We estimated maximum metabolic equivalents (1 metabolic equivalent = 3.5 ml oxygen uptake/kg/min) from the final treadmill speed and grade (29). We dichotomized CRF as low fitness and high fitness corresponding to the lower and the upper 50%, respectively, of the age-specific distribution of treadmill exercise duration from this particular population.

Mortality surveillance. All participants were followed from the date of their baseline examination until their date of death or until December 31, 2003. We computed man-years of exposure as the sum of follow-up time among decedents and survivors. The National Death Index was the primary data source for mortality surveillance, which has been shown to be an accurate method of ascertaining deaths in observational studies, with high sensitivity (96%) and specificity (100%) (30).

Statistical analysis. We described baseline characteristics of the study population by vital status and by thirds of muscular strength. Differences between survivors and decedents were tested using the Student *t* test and chi-square test. Tests for linear trends across muscular strength categories were calculated using general linear models. We used Cox proportional hazards regression to estimate hazard ratios (HRs), 95% confidence intervals (CIs), and mortality rates (deaths per 10,000 person-years of follow-up), according to muscular strength categories. In multivariable analyses, we adjusted for age in model 1 and for age, physical activity (active or inactive), smoking (current smoker or not), alcohol intake (≥ 5 drinks a week or not), body mass index, systolic and diastolic blood pressure, total cholesterol, presence or absence diabetes, abnormal electrocardiogram, and family history of CVD in model 2. Additional analyses were done after further adjustment for CRF in model 3, entered as a continuous variable (treadmill test duration in minutes). A total of 666 participants (44.2%) reported a family history of CVD.

We also examined the combined effects of muscular strength and CRF on all-cause mortality. For this analysis,

we created 6 categories for combinations of strength and CRF on the basis of thirds of muscular strength and dichotomized these into low-fitness and high-fitness groups for CRF. We compared the effect of each combination of strength and fitness status with the reference group (low fitness, low strength). Cumulative hazard plots grouped by exposure suggested no appreciable violations of the proportional hazards assumption. We calculated 2-sided *p* values and considered those < 0.05 as significant. Analyses were done using SAS statistical software, version 9.2 (SAS Institute, Cary, North Carolina).

Results

During an average follow-up of 18.3 years and 27,560 man-years of observation, 183 deaths (12.2%) occurred. Table 1 shows the baseline characteristics of the participants on the basis of vital status and thirds of muscular strength. Muscular strength and exercise test duration and maximum metabolic equivalents were significantly higher in survivors than in decedents. A direct gradient of treadmill test duration across thirds of muscular strength was observed. Age, fasting blood glucose, systolic blood pressure, and prevalence of current smokers, alcohol intake of ≥ 5 drinks weekly, diabetes mellitus, and family history of premature CVD were higher in decedents. Body mass index, levels of glucose, diastolic blood pressure, and prevalence of physical inactivity were higher in those with lower levels of muscular strength.

Table 2 shows age-adjusted death rates and hazard ratios (model 1) for death from all causes; hazard ratios after further adjustment for physical activity, smoking, alcohol intake, body mass index, systolic and diastolic blood pressure, total cholesterol, diabetes, abnormal electrocardiogram, and family history of CVD (model 2); and after additionally adjusting for CRF (model 3). All-cause mortality rates were 1.25 (81.8/65.5) and 1.57 (81.8/52) times greater for those in the lowest third of muscular strength compared with those in the middle and upper thirds of muscular strength, respectively. The age-adjusted results of model 1 showed an inverse risk of death from all causes across incremental thirds of muscular strength ($p < 0.05$ for linear trend). Those participants in the upper muscular strength group had a 36% significantly lower risk of all-cause mortality compared with those in the lower group. After the additional adjustments (model 2), risks of death remained progressively lower with higher levels of muscular strength ($p < 0.05$ for linear trend). Hypertensive men in the upper muscular strength group had a 41% significantly lower risk of all-cause mortality. Finally, after further adjustment for CRF (model 3), the association between muscular strength and risks of death was attenuated ($p = 0.11$ for linear trend), yet those participants in the upper third of muscular strength still had a 34% lower risk of death. Excluding deaths that occurred during the first 3 years of follow-up did not materially change these results.

Table 1 Baseline Characteristics of Hypertensive Men in Aerobics Center Longitudinal Study, 1980 to 2003, According to Vital Status and by Thirds of Muscular Strength

Characteristic	Vital Status				Muscular Strength (Thirds)			
	All (n = 1,506)	Survivors (n = 1,323)	Decedents (n = 183)	p Value*	Lower (n = 499)	Middle (n = 508)	Upper (n = 499)	p Value for Linear Trend
Age, yrs	50.2 ± 7.4	49.7 ± 7.2	54.0 ± 7.9	<0.001	50.5 ± 7.4	50.2 ± 7.4	49.8 ± 7.7	0.33
Body mass index, kg/m ²	26.9 ± 3.7	26.9 ± 3.7	27.1 ± 3.3	0.35	28.2 ± 4.4	26.7 ± 3.1	25.8 ± 3.0	<0.001
Treadmill time, min	17.5 ± 4.8	17.7 ± 4.8	15.8 ± 4.7	<0.001	15.3 ± 4.3	17.6 ± 4.4	19.6 ± 4.8	<0.001
Maximum metabolic equivalents†	11.4 ± 2.4	11.5 ± 2.4	10.6 ± 2.2	<0.001	10.4 ± 2.0	11.4 ± 2.1	12.4 ± 2.5	<0.001
Upper body strength								
kg	66.3 ± 15.0	66.7 ± 14.9	63.0 ± 15.6	0.002	57.3 ± 11.7	65.1 ± 10.8	76.2 ± 15.8	<0.001
kg/kg of body weight	0.8 ± 0.2	0.8 ± 0.2	0.7 ± 0.2	<0.001	0.6 ± 0.1	0.8 ± 0.1	0.9 ± 0.2	<0.001
Lower body strength								
kg	132.3 ± 26.4	132.7 ± 26.0	129.6 ± 29.0	0.15	121.4 ± 26.1	131.9 ± 22.5	143.6 ± 25.7	<0.001
kg/kg of body weight	1.5 ± 0.3	1.6 ± 0.3	1.5 ± 0.2	0.008	1.3 ± 0.2	1.5 ± 0.1	1.8 ± 0.2	<0.001
Composite strength score	0.00	0.03 ± 0.88	-0.23 ± 0.82	<0.001	-0.87 ± 0.45	-0.05 ± 0.33	0.91 ± 0.66	<0.001
Total cholesterol, mg/dl	221.9 ± 43.2	221.1 ± 41.4	227.7 ± 54.5	0.05	222.6 ± 39.1	221.6 ± 49.1	221.5 ± 40.8	0.91
Fasting blood glucose, mg/dl	104.4 ± 20.0	103.6 ± 16.9	110.5 ± 34.7	<0.001	106.8 ± 26.4	103.0 ± 15.4	103.5 ± 16.2	0.005
Blood pressure, mm Hg								
Systolic	131.7 ± 13.9	131.1 ± 13.7	136.1 ± 14.6	<0.001	131.2 ± 13.1	130.9 ± 13.2	133.0 ± 15.3	0.03
Diastolic	89.94 ± 8.5	89.3 ± 8.6	89.9 ± 7.6	0.36	90.1 ± 8.5	88.7 ± 8.0	89.4 ± 8.9	0.03
Physically inactive	339 (22.5)	301 (22.8)	38 (20.8)	0.55	144 (28.9)	123 (24.2)	72 (14.4)	<0.001
Current smokers	220 (14.6)	182 (13.8)	38 (20.8)	0.01	86 (17.2)	65 (12.8)	69 (13.8)	0.11
Alcohol intake ≥5 drinks weekly	812 (53.9)	700 (52.9)	112 (61.2)	0.04	271 (54.3)	261 (51.4)	280 (56.1)	0.31
Baseline medical conditions								
Hypercholesterolemia	450 (29.9)	389 (29.4)	61 (33.3)	0.28	157 (35.1)	145 (28.5)	148 (29.7)	0.59
Diabetes mellitus	93 (6.2)	69 (5.2)	24 (13.1)	<0.001	38 (7.6)	28 (5.5)	27 (5.4)	0.26
Family history of cardiovascular disease	666 (44.2)	562 (42.3)	104 (56.8)	<0.001	215 (43.1)	218 (42.9)	233 (46.7)	0.40

Values are mean ± SD or n (%). *Comparison between survivors and decedents. †Estimated from final treadmill speed and elevation.

Similarly, the results were virtually the same when including those participants who did not achieve 85% of age-predicted maximum heart rate during the treadmill test.

We additionally analyzed the association of muscular strength and risks of all-cause mortality separately for men younger than 60 years of age (n = 1,323, 88%) and 60 years or older (n = 183, 12%), as well as for men with normal weight (n = 479, 32%) and overweight (n = 1,027, 68%), in both cases using the fully adjusted model (except age in the analysis stratified by age, and body mass index in the analysis stratified by weight status). There was no interaction between muscular strength and age (p = 0.28) or between muscular strength and weight status (p = 0.36) in predicting risk of mortality. Among participants age 60 years or older, those in the upper third of muscular strength

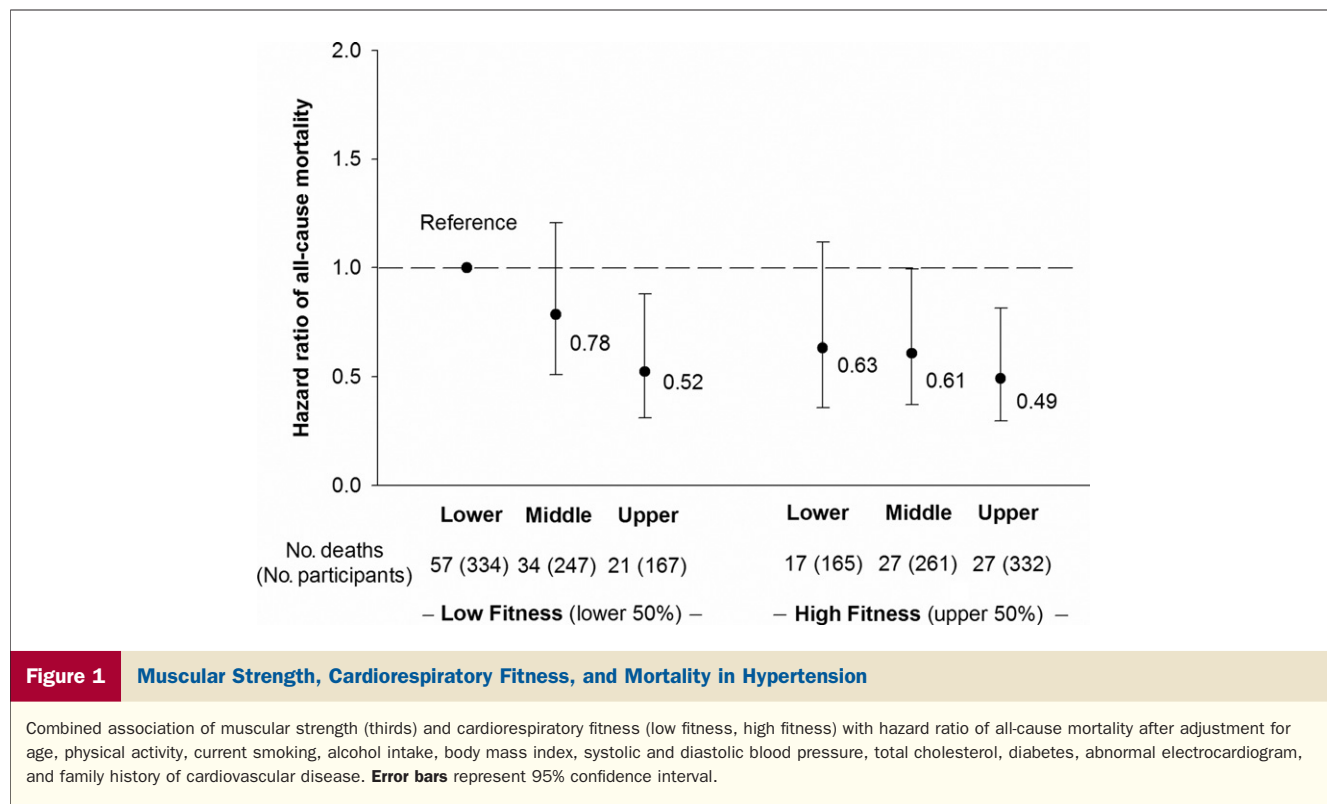
had a 56% lower risk of death compared with those in the lower third (HR: 0.44; 95% CI: 0.20 to 0.98).

Figure 1 shows all-cause mortality risks across combined categories of muscular strength (thirds) and CRF (low and high fitness). There was no significant interaction between muscular strength and CRF in predicting risk of mortality (p = 0.46). Those participants in the low-fitness group and upper third of muscular strength had a 48% lower risk of mortality (HR: 0.52; 95% CI: 0.31 to 0.82) compared with the reference group (low fitness, lower third of muscular strength). Among participants in the high-fitness group, men in the middle and upper thirds of muscular strength had 39% (HR: 0.61; 95% CI: 0.37 to 0.995) and 51% (HR: 0.49; 95% CI: 0.30 to 0.82) lower risks of mortality, respectively, compared with the reference group.

Table 2 Rates and Hazard Ratio for All-Cause Mortality in Hypertensive Men by Thirds of Muscular Strength

Muscular Strength	No. of Deaths (No. of Participants)	Age-Adjusted Rate per 10,000 Person-Yrs	Hazard Ratio (95% Confidence Interval)		
			Model 1*	Model 2†	Model 3‡
Lower	74 (499)	81.8	1.00 (reference)	1.00 (reference)	1.00 (reference)
Middle	61 (508)	65.5	0.80 (0.57-1.12)	0.81 (0.57-1.14)	0.86 (0.60-1.21)
Upper	48 (499)	52.0	0.64 (0.44-0.91)	0.59 (0.40-0.86)	0.66 (0.45-0.98)
p value for linear trend			0.048	0.02	0.11

*Adjusted for age. †Adjusted for age, physical activity (active or inactive), current smoking, alcohol intake (≥5 drinks weekly), body mass index, systolic and diastolic blood pressure, total cholesterol, diabetes, abnormal electrocardiogram, and family history of cardiovascular disease. ‡Adjusted for age, physical activity (active or inactive), current smoking, alcohol intake (≥5 drinks weekly), body mass index, systolic and diastolic blood pressure, total cholesterol, diabetes, abnormal electrocardiogram, family history of cardiovascular disease, and cardiorespiratory fitness (treadmill test duration in min).



Discussion

The primary finding of this study is that a high level of muscular strength was significantly associated with a lower risk of all-cause mortality in hypertensive men, after controlling for potential confounders including CRF. The combined analysis showed that hypertensive men with high levels of both muscular strength and CRF presented the lowest risk of all-cause mortality. This finding extends our previous observation that hypertensive men with at least moderate CRF have a lower risk of mortality (4,5,31). The present study suggests that a high level of muscular strength also provides an additional protective effect, and the reduction in mortality can be higher when hypertensive men have a high level of both muscular strength and CRF.

Several prospective studies have shown that muscular strength is inversely associated with all-cause and cancer mortality (15-23), suggesting the important role of muscular health in the prevention of chronic disease (9). Our study overcomes some limitations of previous reports, such as the use of relatively small muscle groups (mainly handgrip test) (15,16,21,32-35), short-term follow-up (4 to 6 years) (32-35), the inclusion of only older adults (65 years and older) (32,34,35), and the absence of CRF (15,21,32-34). In our study, muscular strength and CRF were moderately correlated (age-adjusted partial $r = 0.42$), suggesting that the association between muscular strength and risk of death works at least partially through different mechanisms than those associated with the protective effect of CRF. The apparent protective effect of muscular strength against risk

of death might be due to muscular strength in itself, to respiratory muscular strength and pulmonary function (36), to muscle fiber type or configuration, or as a consequence of regular physical exercise, specifically resistance exercise. We previously reported a strong and positive association between the frequency of self-reported resistance exercise and maximal muscular strength in men enrolled in the Aerobics Center Longitudinal Study (37). Results from intervention studies indicate that resistance training enhances muscular strength and endurance, muscle mass, functional capacity, daily physical activity, risk profile for CVD, and quality of life (10), all of which are well-known predictors of mortality risk. The benefits of resistance training are evident in men and women; young adults and older individuals; normal weight, overweight, and obese people; and people with or without CVD, including hypertension (7,10).

To the best of our knowledge, this is the first study that relates muscular strength and mortality in the high-risk population of hypertensive men. Being hypertensive is associated with an increased incidence of all-cause and CVD mortality (1). However, this and other studies show that lifestyle factors such as diet (38), regular physical activity (7), CRF (4,5,31), and now muscular strength can be effective in the management of the higher risk in hypertensive patients. According to our results, hypertensive men should follow the recommendations for resistance exercise not only to reduce resting blood pressure (11,12), but also to reduce mortality risk. In fact, the Physical Activity Guidelines for Americans (8) encourage adults to

perform muscle-strengthening activities that involve major muscle groups on ≥ 2 days a week, supervised by a healthcare provider in the case of people with a chronic medical condition.

Study limitations. The results of the present study, however, should be interpreted with caution. The small number of deaths prevents a firm conclusion and does not allow for the examination of the relationship between muscular strength and disease-specific mortality risk in hypertensive men. Studies involving a larger number of deaths should analyze the potential association between muscular strength and CVD mortality in hypertensive people. The composition of the study sample by well-educated white men of middle and upper socioeconomic status and the impossibility of performing a parallel analysis of women need also to be considered. However, the homogeneity of our study group of socioeconomic factors enhances internal validity of our findings because it reduces the likelihood of confounding by these characteristics. In addition, men in the Aerobics Center Longitudinal Study cohort are very similar on key clinical measures such as lipids, glucose, and blood pressure to participants in other large epidemiological studies in the United States (39). We are not aware of biological reasons to believe that the benefits of muscular strength would be different in hypertensive people from other ethnic or socioeconomic groups. Prospective studies among diverse populations and among women are needed.

As another potential limitation, we did not have sufficient information on diet or medication use/adherence to include in our analysis, which may have biased the results through residual confounding. Hypertensive individuals on medication therapy might be more health conscious and have healthier lifestyle habits. However, it seems unlikely that these factors would account for all the observed association between muscular strength and mortality. Future studies should include such information whenever possible. In addition, as we only have baseline data on muscular strength and CRF, we do not know whether changes in any of these variables occurred during follow-up and how this might have influenced the results. It is possible that many men with hypertension were treated at some point in the follow-up interval, and others may have experienced increases/decreases in these exposures.

Despite these limitations, a major strength of this study was the inclusion of objective and standardized maximal tests for muscular strength (upper and lower body) and CRF using highly reliable measurement protocols in a relatively large cohort of hypertensive men with extensive follow-up. Undetected subclinical disease is always a concern in any observational study, but it is less likely to have occurred in our cohort because of the comprehensive physical examination and the clinical assessment completed for each participant. Moreover, participants were healthy enough to achieve at least 85% of age-predicted maximal heart rate during the treadmill test. In addition, excluding deaths

during the first 3 years of follow-up did not alter the results in the current study.

Conclusions

This study found that high levels of muscular strength are associated with a lower risk for all-cause mortality in men with diagnosed hypertension, and this is in addition to the protective effect provided by CRF. Hypertensive men should follow current physical activity guidelines and engage in muscle-strengthening activities that involve major muscle groups, not only to reduce resting blood pressure but also to potentially reduce long-term mortality risk. Hypertensive men can attain even greater reduction in mortality risk if they maintain high levels of both muscular strength and CRF.

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Key Words: cardiorespiratory fitness ■ hypertension ■ mortality ■ muscular strength.

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