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Effects of Cardiorespiratory Fitness on Blood Pressure Trajectory With Aging in a Cohort of Healthy Men

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ABSTRACT

BACKGROUND Although the trajectory of blood pressure (BP) with aging is well known, there is a lack of data on how cardiorespiratory fitness (hereafter referred to as fitness) affects age-associated changes in BP.

OBJECTIVES The objective of the study was to investigate whether fitness alters the aging-BP trajectory.

METHODS A cohort from the Aerobics Center Longitudinal Study totaling 13,953 men between 20 and 90 years of age who did not have hypertension, cardiovascular disease, or cancer completed 3 to 28 (mean of 3.8) follow-up medical examinations between 1970 and 2006. Fitness was measured by a maximal treadmill exercise test. Longitudinal data were analyzed using linear mixed models.

RESULTS Diastolic blood pressure (DBP) tended to increase until nearly 60 years of age, when a decrease was observed. Systolic blood pressure (SBP) tended to increase over all age periods. On multivariate analysis, average SBP increased by 0.30 mm Hg (95% confidence interval: 0.29 to 0.31) with 1-year age increment after adjusting for body fat percent, fitness, resting heart rate, glucose level, triglyceride level, cholesterol level, current smoking, heavy alcohol consumption, and parental history of hypertension. DBP had a yearly increase of 0.14 mm Hg (95% confidence interval: 0.13 to 0.15) before age 60 years. Overall, abnormal SBP (>120 mm Hg) began to occur at approximately 50 years of age and abnormal DBP (>80 mm Hg) began to occur at 60 years of age. Men with higher fitness levels experienced abnormal SBP later than those with low fitness levels.

CONCLUSIONS Our findings underscore the potential modifying effect of fitness on BP trajectory with aging over the male adult life span. Improving fitness levels might extend the normal SBP and DBP ranges, delaying the development of hypertension. (J Am Coll Cardiol 2014;64:1245–53) © 2014 by the American College of Cardiology Foundation.

Approximately one-third of U.S. adults (~68 million) have high blood pressure (BP), which significantly increases the risk of cardiovascular disease (CVD), the leading cause of death in the United States (1) and worldwide (2,3). High BP is also a risk factor for other chronic diseases, such as diabetes (4) and renal disease (5). There is substantial evidence that diet and physical activity are the major modifiable lifestyle factors for preventing increases in BP (6,7).

During the past century, progressively elevated BP was believed to be part of the human aging process

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ABBREVIATIONS AND ACRONYMS

BMI = body mass index
BP = blood pressure
CI = confidence interval
CVD = cardiovascular disease
DBP = diastolic blood pressure
PP = pulse pressure
RIM = random intercept model
SBP = systolic blood pressure

(8,9) in the industrialized world, even though little or no age-related increase in BP is observed in some populations, including American Indian populations such as the Yanomamo and Xingu (10,11). The Framingham Heart Study showed that the aging patterns of elevated BP differed for systolic blood pressure (SBP) and diastolic blood pressure (DBP); SBP increased continuously from 30 years of age, whereas DBP increased until midlife and then decreased (12–14).

Previous studies have shown that increased cardiorespiratory fitness (hereafter referred to as fitness) levels result in lowered BP in an inverse relationship that varies across age strata (15–17). However, little knowledge exists regarding the impact of fitness on age-associated changes in BP, and the mechanism is currently unclear. Identifying the age-related BP trajectory and exploring factors that modify the trajectory are important public health goals with significant clinical implications.

SEE PAGE 1254

In this study, we evaluated the effects of aging and fitness on BP (SBP, DBP, and pulse pressure [PP]) using data from the Aerobics Center Longitudinal Study. The purpose of the study was to define the longitudinal, aging BP trajectory and determine whether fitness is an independent modifier of the age-associated BP trajectory.

METHODS

STUDY POPULATION. The Aerobics Center Longitudinal Study is a large cohort study of healthy adults. The majority (95%) of the study population is white, graduated from college, is employed in professional or executive occupations, and comes from middle to high socioeconomic strata. The current analytical sample consisted of 13,953 men between 20 and 90 years of age who had at least 3 preventive medical evaluations at the Cooper Clinic in Dallas, Texas, between 1970 and 2006. These men completed between 3 and 28 evaluations (mean of 3.8) for a total of 56,140 observations. All participants in this sample had complete data on SBP and DBP, normal resting and exercising electrocardiograms, and a body mass index (BMI) ≥18.5 kg/m^2 and were able to reach 85% of age-predicted maximal heart rate during their treadmill tests. No subjects had a history of myocardial infarction, stroke, cancer, or hypertension at baseline. Participants with a history of self-reported hypertension during any visit were excluded to remove treatment effects on BP levels. The Cooper Institute Institutional Review Board approved the study protocol annually, and all participants gave informed consent for the baseline examination and follow-up study.

CLINICAL EXAMINATIONS. The clinical examination included a physical examination, anthropometry measurements, fasting blood chemistry analysis, resting BP, symptom-limited maximal exercise test for the measurement of fitness, and a standardized questionnaire on personal and family medical history. All measures were obtained after subjects had fasted overnight for at least 12 h.

Resting SBP and DBP were measured with the participant in a seated position after at least a 5-min rest; trained technicians used mercury manometers and followed a standard procedure to measure SBP and DBP (18). More than 2 readings were taken, and the average was used in the analysis. PP was defined as the difference between SBP and DBP. Hypertension was defined as SBP ≥140 mm Hg and/or DBP ≥90 mm Hg. Fasting glucose and lipid profiles were analyzed by using automated laboratory techniques at the Cooper Clinic, which meets the quality control standards of the Centers for Disease Control and Prevention Lipid Standardization Program (18). Hypercholesterolemia was defined as a total cholesterol concentration ≥240 mg/dl or physician diagnosis. Diabetes was defined as a fasting glucose concentration ≥126 mg/dl, use of insulin, or physician diagnosis.

Age, smoking status, and alcohol consumption status were obtained by self-administered questionnaire. BMI was calculated from measured weight and height in accordance with standard procedures. Waist circumference was measured at the level of the umbilicus with a plastic tape measure. Physical inactivity was assessed by self-report and defined as reporting no physical activity during leisure time in the 3 months before the examination.

Body fat percent was assessed by hydrostatic weighing, skin fold thickness measurements, or both. When both methods were available, hydrostatic weighing was preferred. Cardiorespiratory fitness was assessed by using a Balke (19) maximal treadmill exercise test. Total treadmill time, which is highly correlated with maximal oxygen uptake, was used as an index of aerobic power. All participants were classified into low (<33rd percentile), moderate (33rd to 66th percentile), or high fitness categories (>66th percentile) according to the distribution of age-specific treadmill time. Information about measuring body fat percent and fitness is provided in detail elsewhere (20).

STATISTICAL ANALYSIS. Means and SDs were calculated for continuous variables, and percents were calculated for categorical variables. The random intercept model (RIM), a simple version of the linear mixed model (21,22), was used to analyze the longitudinal data. The rationale behind the linear mixed model is that it can accommodate an unbalanced study design with unequally spaced repeated measures over time. We used age as the measure of time for growth in each subject. The random intercept model takes into account within-subject measure dependency and also variability in subject-specific intercepts not explained by the independent variables included in the model. Conditional on the unobserved random intercept, the observations in each subject are assumed to be independent. The correlations among repeated measurements of the same subject can be obtained through a specified structure. Considering that only a few measurements are unequally spaced over time, the correlation structure is modeled by an autoregressive process of order 1. The dependent variables for each RIM analysis were BP (SBP, DBP, and PP). All the models were fitted after adjusting for the baseline examination time, which took cohort effects into account. We first examined the longitudinal change in BP associated with aging. Both linear and quadratic models were examined. We then evaluated the influence of body fat percent on the age-BP association, because it has been significantly linked to BP (23). Next, we investigated the independent influence of fitness and body fat percent on age-related changes in BP. Finally, we accounted for time-varying covariates, including waist circumference, smoking status, fasting glucose level, and cholesterol level. A log likelihood ratio test was used to determine if the model improved the fit (24,25). In addition, the Bayesian information criterion (24) and Akaike information criterion (25) were used to assess the balance between achieving a good fit of the model to the data and obtaining precise parameter estimates to compare models. Each regression coefficient was tested with a z-statistic to determine if it was significantly different from 0. Statistical tests were 2 sided: $p < 0.05$ indicated statistical significance. We fitted all the models using the function *lme* in the package *nlme* in R (version 3.0.1). This R function implements 2 likelihood-based methods: maximum likelihood and restricted maximum likelihood. The restricted maximum likelihood estimation method is preferred in most cases, whereas the likelihood ratio test comparing the full and reduced models is only valid with maximum likelihood estimation.

TABLE 1 Baseline Characteristics for Male Participants According to Fitness Groups: Aerobics Center Longitudinal Study, 1970–2006

		Level of Fitness			
	Overall (N = 13,953)	Low (n = 1,532)	Moderate (n = 5,416)	High (n = 7,005)	p Value for Linear Trend
Age, yrs	42.98 ± 8.84	41.44 ± 7.72	42.76 ± 8.49	43.49 ± 9.29	<0.001
Height, cm	179.26 ± 6.48	178.33 ± 6.56	179.23 ± 6.49	179.48 ± 6.43	<0.001
Weight, kg	83.17 ± 11.86	90.83 ± 16.44	84.89 ± 11.64	80.16 ± 9.60	<0.001
Body mass index, kg/m^2	25.85 ± 3.21	28.50 ± 4.56	26.4 ± 3.1	24.85 ± 2.41	<0.001
Waist circumference, cm	92.41 ± 9.59	102.83 ± 12.49	95.36 ± 9.03	89.06 ± 7.67	<0.001
Body fat percent	20.39 ± 6.28	25.40 ± 6.60	22.13 ± 5.7	18.01 ± 5.53	<0.001
Systolic blood pressure, mm Hg	119.33 ± 11.94	120.94 ± 12.75	119.44 ± 11.56	118.89 ± 12.01	<0.001
Diastolic blood pressure, mm Hg	79.68 ± 8.73	81.55 ± 9.08	80.37 ± 8.80	78.74 ± 8.47	<0.001
Treadmill time duration, min	18.91 ± 4.61	12.09 ± 2.12	16.44 ± 2.19	22.32 ± 3.35	<0.001
Maximal metabolic equivalents	12.12 ± 2.29	8.93 ± 0.98	10.91 ± 1.02	13.75 ± 1.85	<0.001
Resting heart rate	59.50 ± 10.34	66.76 ± 10.09	62.43 ± 9.69	55.66 ± 9.23	<0.001
Fasting plasma glucose level, mg/dl	99.07 ± 13.59	102.55 ± 18.09	99.7 ± 14.49	97.81 ± 11.37	<0.001
Triglyceride level, mg/dl	127.52 ± 94.34	177.26 ± 128.54	141.26 ± 100.04	105.92 ± 72.17	<0.001
Total cholesterol level, mg/dl	207.98 ± 39.13	218.42 ± 42.16	212.33 ± 39.26	202.31 ± 37.40	<0.001
Current smoker	14.9	27.3	18.3	9.6	<0.001
Heavy alcohol consumption*	6.3	4.6	5.6	7.2	<0.001
Physical inactivity	30.3	68.4	41.3	13.5	<0.001
Diabetes†	3.4	7.1	3.7	2.4	<0.001
Hypercholesterolemia‡	25.2	32.8	27.9	21.4	<0.001
Parental history of hypertension	13.2	9.9	12.2	14.8	<0.001

Values are mean ± SD or %. *Defined as more than 14 alcoholic drinks per week for men. †Defined as a fasting glucose level ≥126 mg/dl, physician-diagnosed diabetes, or use of insulin. ‡Defined as a total cholesterol level ≥240 mg/dl or physician-diagnosed hypercholesterolemia.

RESULTS

The baseline characteristics of the current study sample according to the 3 baseline fitness levels are described in Table 1. The overall sample size and each specific sample size are provided on the basis of fitness levels. Overall, participants in the high fitness category had more favorable baseline characteristics, including lower BMI, waist circumference, body fat percent, resting heart rate, triglyceride level, and cholesterol level, compared with participants with lower fitness levels. The groups with lower fitness levels had higher percents of current smokers, were more physically inactive, and were likely to have diabetes and hypercholesterolemia. However, the percents of participants with heavy alcohol consumption and a parental history of hypertension displayed opposite trends across the fitness levels.

On the basis of the estimated correlation matrix, we found high correlations between fitness and body fat percent, waist circumference, and resting heart rate, which could lead to the issue of multicollinearity and affect the relationship of fitness with BP trajectories with aging. To reduce multicollinearity, 3 RIM models were fitted with fitness as a predictor and body fat percent, waist circumference, and resting heart rate as a response, respectively. The residuals of those 3 variables were the variations unexplained by fitness; they were then added into the multivariate model with other covariates. Although it has been shown that fitness has a nonlinear relationship with aging (26), we discovered that fitness levels varied substantially across all age groups. Therefore, we did not standardize fitness by age.

The RIM results for SBP, DBP, and PP trajectories with aging, after adjusting for the other covariates, are presented in Tables 2 to 4. We found that the SBP trajectory with aging was linear, whereas DBP and PP were nonlinear. SBP increased by 0.30 mm Hg (95% confidence interval [CI]: 0.29 to 0.31) with each year of age (Table 2). Body fat percent was added into model II and the β coefficient for age dropped significantly to 0.25, indicating that body fat percent is a significant confounder and independently correlates with SBP. After controlling for body fat percent, SBP increased by 0.25 mm Hg (95% CI: 0.24 to 0.26) with each 1-year increase in age. When fitness and age × fitness interaction were added to model III, model fit was improved on the basis of Akaike information criterion and Bayesian information criterion values. Model III showed that fitness was negatively associated with SBP and that the age × fitness interaction was significant. Finally, all covariates, including waist circumference, resting heart rate, fasting glucose level, triglyceride level, cholesterol level, smoking status, alcohol consumption status, and parental history of hypertension,

TABLE 2 Partial Regression Coefficients (β) and SEs for the Systolic Blood Pressure Predictor Variables in the Random Intercept Model Analyses: Aerobics Center Longitudinal Study, 1970–2006

	Model I			Model II			Model III			Model IV		
Variable	β	SE	p Value	β	SE	p Value	β	SE	p Value	β	SE	p Value
Fixed effects												
Intercept	118.78	0.17	<0.001	114.67	0.27	<0.001	118.48	0.18	<0.001	111.05	0.62	<0.001
Age	0.30	0.007	<0.001	0.25	0.007	<0.001	0.23	0.008	<0.001	0.31	0.008	<0.001
Date of baseline examination	0.00016	0.00003	<0.001	0.00013	0.00003	<0.001	0.00014	0.00003	<0.001	0.00022	0.00003	<0.001
Body fat percent				0.20	0.01	<0.001	0.15	0.01	<0.001	0.05	0.02	0.0051
Fitness							−0.60	0.03	<0.001	−0.35	0.03	<0.001
Age × fitness							−0.02	0.003	<0.001	−0.03	0.003	<0.001
Waist circumference										0.14	0.0099	<0.001
Resting heart rate										0.13	0.007	<0.001
Fasting plasma glucose level										0.04	0.005	<0.001
Triglyceride level										0.006	0.0007	<0.001
Total cholesterol level										0.009	0.002	<0.001
Current smoker										−1.56	0.19	<0.001
Heavy alcohol consumption										1.76	0.22	<0.001
Parental history of hypertension										1.86	0.16	<0.001
Random effects												
SD intercept (95% CI)	7.78 (7.63-7.94)			7.71 (7.55-7.88)			7.80 (7.64-7.97)			7.62 (7.45-7.79)		
SD error (95% CI)	9.26 (9.18-9.34)			9.15 (9.07-9.24)			9.10 (9.01-9.18)			8.74 (8.65-8.83)		

Body fat percent, waist circumference, and resting heart rate were normalized by fitness.
CI = confidence interval; SD error = SE of the linear mixed model; SD intercept = SD of the individual variance of the random part of the model.

TABLE 3 Partial Regression Coefficients (β) and SEs for the Diastolic Blood Pressure Predictor Variables in the Random Intercept Model Analyses: Aerobics Center Longitudinal Study, 1970–2006

	Model I			Model II			Model III			Model IV		
Variable	β	SE	p Value	β	SE	p Value	β	SE	p Value	β	SE	p Value
Fixed effects												
Intercept	78.53	0.12	<0.001	73.46	0.19	<0.001	78.50	0.12	<0.001	74.16	0.45	<0.001
Age	0.16	0.005	<0.001	0.12	0.005	<0.001	0.11	0.005	<0.001	0.14	0.006	<0.001
Age^2	−0.003	0.0003	<0.001	−0.002	0.0003	<0.001	−0.003	0.0003	<0.001	−0.002	0.0004	<0.001
Date of baseline examination	0.0003	0.00002	<0.001	0.0002	0.00002	<0.001	0.0003	0.00002	<0.001	0.0002	0.00002	<0.001
Body fat percent				0.25	0.008	<0.001	0.20	0.009	<0.001	0.08	0.01	<0.001
Fitness							−0.61	0.02	<0.001	−0.49	0.02	<0.001
Waist circumference										0.12	0.007	<0.001
Resting heart rate										0.13	0.005	<0.001
Fasting plasma glucose level										0.007	0.003	0.0338
Triglyceride level										0.005	0.0006	<0.001
Total cholesterol level										0.02	0.001	<0.001
Current smoker										−1.02	0.14	<0.001
Heavy alcohol consumption										1.37	0.17	<0.001
Parental history of hypertension										1.39	0.12	<0.001
Random effects												
SD intercept (95% CI)	5.11 (4.99–5.23)			4.99 (4.87–5.12)			5.02 (4.91–5.13)			4.84 (4.72–4.96)		
SD error (95% CI)	6.90 (6.84–6.96)			6.79 (6.73–6.86)			6.77 (6.71–6.83)			6.59 (6.53–6.66)		

Abbreviations as in Table 2.

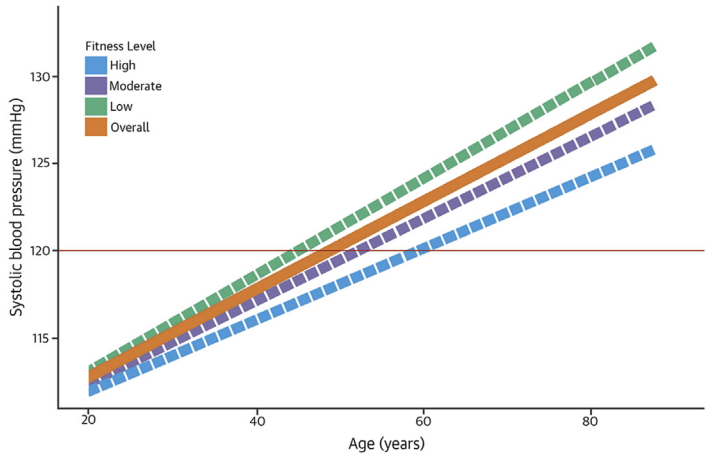
were included in model IV. The results showed that age, body fat percent, waist circumference, resting heart rate, fasting glucose level, triglyceride level, cholesterol level, alcohol consumption status, and parental history of hypertension were all positively associated with SBP. In contrast, smoking status was inversely associated with SBP. The interaction term of age × fitness was still significant in model IV.

Table 3 shows that DBP was positively associated with age, body fat percent, waist circumference, resting heart rate, fasting glucose level, triglyceride

TABLE 4 Partial Regression Coefficients (β) and SEs for the Pulse Pressure Predictor Variables in the Random Intercept Model Analyses: Aerobics Center Longitudinal Study, 1970–2006

	Model I			Model II			Model III			Model IV		
Variable	β	SE	p Value	β	SE	p Value	β	SE	p Value	β	SE	p Value
Fixed effects												
Intercept	38.93	0.128	<0.0001	39.63	0.22	<0.0001	38.81	0.13	<0.0001	33.81	0.54	<0.0001
Age	0.12	0.005	<0.0001	0.12	0.006	<0.0001	0.13	0.006	<0.0001	0.16	0.007	<0.0001
Age^2	0.014	0.0004	<0.0001	0.013	0.0004	<0.0001	0.014	0.0004	<0.0001	0.015	0.0004	<0.0001
Date of baseline examination	−0.00009	0.00002	<0.0001	−0.00007	0.00002	<0.0001	−0.00008	0.00002	<0.0001	0.00005	0.00002	0.0185
Body fat percent				−0.04	0.009	<0.0001	−0.02	0.01	<0.0001	−0.03	0.02	0.0949
Fitness							0.17	0.02	<0.0001	0.33	0.03	<0.0001
Waist circumference										0.05	0.009	<0.0001
Resting heart rate										0.02	0.006	0.0026
Fasting plasma glucose level										0.04	0.004	<0.0001
Triglyceride level										0.001	0.0007	0.1565
Total cholesterol level										−0.002	0.002	0.2814
Current smoker										−0.55	0.17	0.001
Heavy alcohol consumption										0.58	0.20	0.0036
Parental history of hypertension										0.81	0.15	<0.0001
Random effects												
SD intercept (95% CI)	4.92 (4.79–5.04)			4.92 (4.79–5.06)			4.90 (4.77–5.03)			4.86 (4.71–5.02)		
SD error (95% CI)	8,47 (8.41–8.53)			8.41 (8.34–8.48)			8.41 (8.35–8.48)			8.34 (8.27–8.42)		

Abbreviations as in Table 2.



CENTRAL ILLUSTRATION **Systolic Blood Pressure Trajectories With Aging in Healthy Men by Fitness Levels**

Trajectories of the overall sample **(orange)** and low **(green)**, moderate **(purple)**, and high fitness levels **(blue)** are provided, assuming a constant 20.31% body fat. The **solid orange horizontal line** represents the cutoff point of 120 mm Hg for a pre-hypertension level of systolic blood pressure.

level, cholesterol level, alcohol consumption status, and parental history of hypertension. Inverse associations were observed between DBP and current smoking and age squared. Additionally, DBP was inversely related to age squared, indicating a quadratic age-DBP pattern. After adjusting all covariates, DBP still maintained a positive association with age (0.14 mm Hg [95% CI: 0.13 to 0.15]). However, no significant interaction between age and fitness was found for changes in DBP.

The pattern of PP is opposite that of DBP, with a much steeper rate of increase after approximately 50 years of age. The interaction term of age × fitness for PP was negative but not statistically significant and thus was not included in our models. **Table 4** summarizes the PP data, showing the curvilinear association of PP with aging. After the multivariate adjustment, PP increased by 0.16 mm Hg (95% CI: 0.15 to 0.17).

To better visualize the effect of fitness on this trajectory, we provided the estimated SBP trajectory with aging and corresponding 95% confidence intervals for participants with 3 different fitness levels, assuming a constant body fat percent residual (−0.06, mean of the residual) and the same baseline examination time in model III. The 3 levels were chosen on the basis of median values from the low (<33rd percentile), moderate (33rd to 66th percentile), or high (>66th percentile) fitness categories. The results for SBP are shown in the **Central Illustration**. We also provided the overall BP trajectory with aging in model II, assuming the same baseline examination time and a constant body fat percent of 20.31. Constant body fat percent was calculated on the basis of the normalization equation with a body fat percent residual of −0.06 and fitness equivalent to mean of the fitness. The **Central Illustration** shows that age and SBP interact at approximately 20 years of age, indicating that the relationship between SBP and aging changes across 3 fitness levels and that fitness is a protective factor for the SBP aging trajectory after 20 years of age.

DISCUSSION

There were several key findings in this prospective, population-based cohort study. First, BP is inversely associated with fitness levels. People in higher fitness categories had lower BP than those in lower fitness categories. Second, the interaction between age and fitness was significant for the SBP trajectory but not for DBP, which partially confirmed our hypothesis that fitness is an effect modifier for the SBP aging trajectory. This finding also indicated that fitness is likely to modify SBP but not DBP. Third, body fat percent had a strong confounding effect. However, after adjusting for body fat percent, the SBP and DBP aging trajectories were not changed significantly, supporting our hypothesis that the age-BP trajectory was independent of body fat percent. Finally, the SBP trajectory increased linearly with age, whereas the DBP trajectory had a nonlinear relationship with aging. These overall trend findings were consistent with previous cohort studies on BP trajectory over the life span but the amounts of change were different, perhaps due to population differences (10,12,27).

Arterial and arteriolar stiffness are the main factors contributing to the increase in BP with aging. Previous studies showed that aortic stiffening with age is mainly caused by elastin fiber fracture, with stresses transferred to collagenous elements in an aorta that becomes progressively dilated (28,29), and by vascular aging manifestations, displayed at the levels of large elastic arteries by arteriosclerosis originating from a gradual mechanical senescence of fibrosis and calcification of elastic fibers (30,31). However, there is significant heterogeneity in this process among different arteries because not all arterial trees exhibit the same age-dependent stiffening (32). Our results showed that in a large cohort of healthy men, for each increase in age of 1 year, SBP linearly increased by 0.30 mm Hg, with an SE

of 0.0007 mm Hg, and DBP increased quadratically by 0.14 mm Hg, with an SE of 0.006 mm Hg, consistent with a prior study (12). The current findings are in agreement with previous studies (12,14) showing that DBP was quadratically associated with aging and that DBP decreased with aging after 60 to 65 years of age. Although the potential mechanism remains unclear, several possible explanations were proposed, including a theory of "burned out" diastolic hypertension and "selective survival." However, Framingham Heart Study investigators found that after "burned out" diastolic hypertension and "selective survival" were removed, DBP still had a quadratic shape (14), leading them to suggest increasing large artery stiffness as the most likely explanation. Because PP might act as a surrogate measure of arterial stiffness, we also examined the longitudinal aging trajectory of PP (**Table 4**). We found that PP increased steeply after approximately 50 years of age, suggesting that arterial stiffness becomes severe with aging. In addition, the quadratic nature of DBP among all categorized BP groups, including the lowest BP group from the Framingham Heart Study, might cancel out the age-related physical fitness relationship. However, this potential mechanism needs further investigation.

Epidemiological studies have consistently shown that fitness is inversely and independently associated with metabolic syndrome, a cluster of CVD risk factors (33,34). Additional evidence shows that physical activity has a dose-dependent relationship with fitness (35). Therefore, fitness plays an important role in the age-BP trajectory. Our results showed that SBP becomes >120 mm Hg at approximately 46 years of age for those in the low fitness level and at 54 years of age for those in the high fitness level. In contrast, at approximately 42 years of age, DBP becomes >80 mm Hg for those at the low fitness level, which does not occur until advanced ages (beyond 90 years) for those at a high fitness level. This suggests that highly fit men are likely to reach abnormal SBP values about a decade later than men in the low fitness category, implying that improving fitness levels may reduce the duration of elevated SBP (36). Although much studied, the physiological mechanism for how BP is lowered by fitness remains unclear. Previous studies proposed that improved endothelial function, with reduction in early wave reflection due to physical activity, could result in lower SBP at a higher level of fitness (37–39). These data have important clinical implications, particularly considering that elevated regular physical activity and aerobic exercise yield important reductions in SBP and DBP in adults. Mean reductions in resting BP ranged from 2 to 5 mm Hg for resting SBP and 2 to 3 mm Hg for resting DBP (40,41). Although these reductions in BP may appear small, they are clinically significant because it has been estimated that as little as a 2-mm Hg reduction in population average resting SBP would reduce coronary heart disease mortality by 4%, while a reduction of 5 mm Hg would reduce coronary heart disease mortality by 9% (36).

The key strength of this study is its design, which included longitudinal measures of SBP, DBP, and other time-varying covariates so that BP trajectories with aging could be assessed. Another advantage is the relatively large sample size, because it provided stable estimates with small SEs. The third strength is that instead of only using BMI, which may not reflect the increased risk of body fatness (42), we used body fat percent to determine body composition; nevertheless, we did not separate visceral from subcutaneous adiposity, which may have different impacts on CVD risk. Finally, we used the RIM method to quantify SBP and DBP trajectories with age by incorporating the unequal-spaced repeated measurements. This RIM method also included random intercepts to account for within-subject dependency and variability in subject-specific intercepts not explained by the independent variables included in the model.

STUDY LIMITATIONS. Several limitations should be acknowledged. The most important concern in longitudinal study design is losses to follow-up. However, this was studied in the Aerobics Center Longitudinal Study and was not a serious problem. Another limitation is that there is no information on antihypertensive medication status. We thus excluded those who reported a history of hypertension at baseline and each follow-up visit. Among these initially hypertension-free men, 1,146 developed hypertension during follow-up, with incidence rates across the low, moderate, and high fitness groups of 11.2%, 9.3%, and 6.7%, respectively. This again shows the association of higher fitness with a lower rate of developing hypertension, as we have reported previously (43).

Because of concerns about the effect of medication on BP trajectory, men who developed hypertension during follow-up were excluded from the analysis. To determine the implications of these exclusions on the results, we repeated the analysis and included the observations from those who developed hypertension during follow-up (Online Tables 1 to 3, Online Figure 1). Although no significant difference between the **Central Illustration** and Online Figure 1 was

observed, the overall line in Online Figure 1 was shifted slightly back, which might indicate that men who developed hypertension received antihypertensive therapy to lower their BP, resulting in a delay in reaching the SBP level of 120 mm Hg. Thus, the aging-BP trajectory was no longer natural. This was also a concern in the Framingham Heart Study (14); the investigators stated that the efficacy of treating hypertension was not well established when the study started in 1948, which offered the unique opportunity to study the effect of the untreated BP-aging trajectory. Because the current study started in the 1970s, when antihypertensive therapy was widely administered, we excluded these men from the main analysis due to this concern. Heart rate was included in the multivariate models to further control the possible effect of beta-adrenergic blocking agents on BP, because these agents have been used since early in this study. In addition, because we were limited to available clinical measurements obtained at irregular clinical intervals, we cannot eliminate the possibility of confounding by unmeasured or unknown factors. The current study includes relatively healthy men who were primarily white and of middle to upper socioeconomic status. We should therefore be cautious about generalizing these results to other populations, including those with pre-existing conditions.

CONCLUSIONS

Our findings underscore the potential effects of fitness on SBP trajectories with aging over the adult life span. Promoting fitness to extend the duration of normal SBP might reduce the potential risk of developing hypertension, CVD, and other BP-related chronic diseases, as well as reduce medical costs, major morbidity, and mortality. Because regular physical activity is the primary and most modifiable determinant of fitness level, our results underscore the potential importance of increasing regular physical activity to prevent the aging-related progressive rise in BP.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Human aging is associated with progressively increasing blood pressure. Better cardiorespiratory fitness can lower systolic and diastolic blood pressure, and the inverse relationship between fitness and blood pressure varies with age.

TRANSLATIONAL OUTLOOK: The mechanisms by which fitness modifies the relationship between aging and blood pressure deserves further investigation, particularly in those with hypertension or other forms of cardiovascular disease.

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KEY WORDS aging, blood pressure, cardiorespiratory fitness, cohort study

APPENDIX For supplemental tables and a figure, please see the online version of this paper.