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ORIGINAL RESEARCH

Association of Blood Pressure Responses to Submaximal Exercise in Midlife With the Incidence of Cardiovascular Outcomes and All-Cause Mortality: The Framingham Heart Study

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BACKGROUND: Few studies examined the associations of midlife blood pressure (BP) responses to submaximal exercise with the risk of cardiovascular outcomes and mortality in later life.

METHODS AND RESULTS: We evaluated 1993 Framingham Offspring Study participants (mean age, 58 years; 53.2% women) attending examination cycle 7. We related BP responses to submaximal exercise with prevalent subclinical cardiovascular disease (CVD) using multivariable linear regression models. We also related BP responses to submaximal exercise to the incidence of hypertension, CVD, and all-cause mortality using Cox proportional hazards regression models. Each SD increment of exercise BP was associated with higher log-transformed left ventricular mass (systolic blood pressure [SBP], β=0.02, *P*=<0.001; diastolic blood pressure [DBP], β=0.01, *P*=0.004) and carotid intima-media thickness (SBP, β=0.08, *P*=<0.001). Rapid BP recovery (per 1 SD increment) was associated with lower log left ventricular mass ($SBP_{recovery}$; β=−0.03, *P*=<0.001) and carotid intima-media thickness ($SBP_{recovery}$, β=−0.07, *P*=0.003; $DBP_{recovery}$, β=−0.09, *P*=0.003). Additionally, Each SD increment of exercise BP was associated with a higher risk of incident hypertension (SBP, hazard ratio [HR], 1.40; 95% CI, 1.20–1.62; DBP, HR, 1.24; 95% CI, 1.11–1.40) and CVD (DBP, HR, 1.15; 95% CI, 1.02–1.30). Finally, the multivariable-adjusted HR for each 1-SD increment of BP recovery was 0.46 ($SBP_{recovery}$, 95% CI, 0.38–0.54) and 0.55 ($DBP_{recovery}$, 95% CI, 0.45–0.67) for hypertension; 0.80 ($SBP_{recovery}$, 95% CI, 0.69–0.93) for CVD; and 0.76 ($SBP_{recovery}$, 95% CI, 0.65–0.88) for all-cause mortality.

CONCLUSIONS: Higher submaximal exercise BP and impaired BP recovery after submaximal exercise in midlife may be markers of subclinical and clinical CVD and mortality in later life.

Key Words: cardiovascular disease ■ exercise blood pressure ■ hypertension ■ mortality ■ subclinical disease

Blood pressure (BP) responses to exercise are significant markers of cardiovascular disease (CVD) and mortality risk in young to middle-aged adults. A number of studies have examined the association between BP responses to exercise in people aged 40 to 55 years and the risk of developing hypertension,[1–4] stroke,[5] myocardial infarction,[6,7] CVD,[8,9] and cardiovascular death.[10,11] However, limited evidence exists on the associations of exercise BP measures in midlife or later (aged 55 years or older) and risk of outcome events in later life. Additionally, prior studies focused primarily on the relation of systolic blood pressure (SBP) response to exercise with cardiovascular outcomes.[5–7,10–12] Fewer investigators

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CLINICAL PERSPECTIVE

What Is New?

- We observed significant associations of higher exercise blood pressure and delayed blood pressure recovery after submaximal exercise with a higher risk of hypertension, subclinical and clinical CVD, and all-cause mortality in middle-aged to older adults.

What Are the Clinical Implications?

- Submaximal exercise blood pressure and blood pressure recovery after submaximal exercise in midlife may provide important prognostic information on the risk classification of new-onset of hypertension, cardiovascular disease, and mortality in later life.

Nonstandard Abbreviations and Acronyms

BMI	body mass index
BP	blood pressure
CVD	cardiovascular disease
CIMT	carotid intima-media thickness
DBP	diastolic blood pressure
FOS	Framingham Offspring Study
HDL-C	high-density lipoprotein cholesterol
HR	heart rate
ICA	internal carotid artery
LVM	left ventricular mass
SBP	systolic blood pressure
TC	total cholesterol

evaluated the prognostic significance of exercise diastolic blood pressure (DBP) or BP recovery after exercise in relation to incident hypertension[1] and CVD events.[8,12]

Accumulating evidence suggests that the SBP response to exercise is associated with indicators of subclinical CVD, including left ventricular mass (LVM),[13,14] and carotid intima-media thickness (CIMT)[15] in young or middle-aged adults. However, limited evidence exists regarding these associations in midlife in community-dwelling adults. Additionally, little is known about the relation of DBP response to exercise and BP recovery after exercise with indicators of subclinical CVD. Given that presence of subclinical CVD is directly associated with the risk of development of cardiovascular outcomes,[16–18] examining the relation between BP responses to exercise and prevalence of subclinical CVD may help identify individuals at risk of cardiovascular outcomes later in life.

Accordingly, we hypothesized that favorable BP responses to submaximal exercise and rapid BP recovery after exercise in midlife are associated with (1) lower burden of subclinical CVD components cross sectionally; and (2) a lower risk of hypertension, CVD, and all-cause mortality prospectively.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Sample

The FOS (Framingham Offspring Study) is a longitudinal community-based study established in 1971 and includes 5124 men and women who were children and spouses of children of the original Framingham cohort.[19] Among 3539 FOS participants who attended the seventh examination cycle (1998–2001), 217 participants did not undergo the submaximal exercise test, and 881 participants were excluded because of prior coronary heart disease and presence of a disability that could limit the exercise test performance. Thus, 2441 participants performed the submaximal exercise test and were eligible for the present investigation.

Of the 2441 eligible participants, we excluded those who were unable to complete the submaximal exercise test (n=290), had prior cerebrovascular or peripheral vascular disease (n=49), had unavailable data on exercise BP variables (n=74), or were missing key covariates (n=35) at baseline. We then used this final sample to examine the association of BP responses to submaximal exercise with CVD and all-cause mortality (sample 1; n=1993). To investigate the relation of exercise BP responses to submaximal exercise with the incidence of hypertension, we additionally excluded 754 participants who had a history of hypertension at baseline (n=598) or unavailable data on hypertension status (n=156) after examination cycle 7 (sample 2; n=1239).

The cross-sectional associations between BP responses to submaximal exercise and indicators of subclinical CVD, including LVM and CIMT, were examined using 2 different subsamples of sample 1 (n=1993). Among 1993 available participants, we excluded those with missing data on LVM (n=333), or CIMT (n=459) resulting in final sample sizes of 1660 (LVM; sample 3), 1534 (CIMT; sample 4). The Consolidated Standards of Reporting Trials diagram of participant flow is shown in the Figure. The study was approved by the Boston University Medical

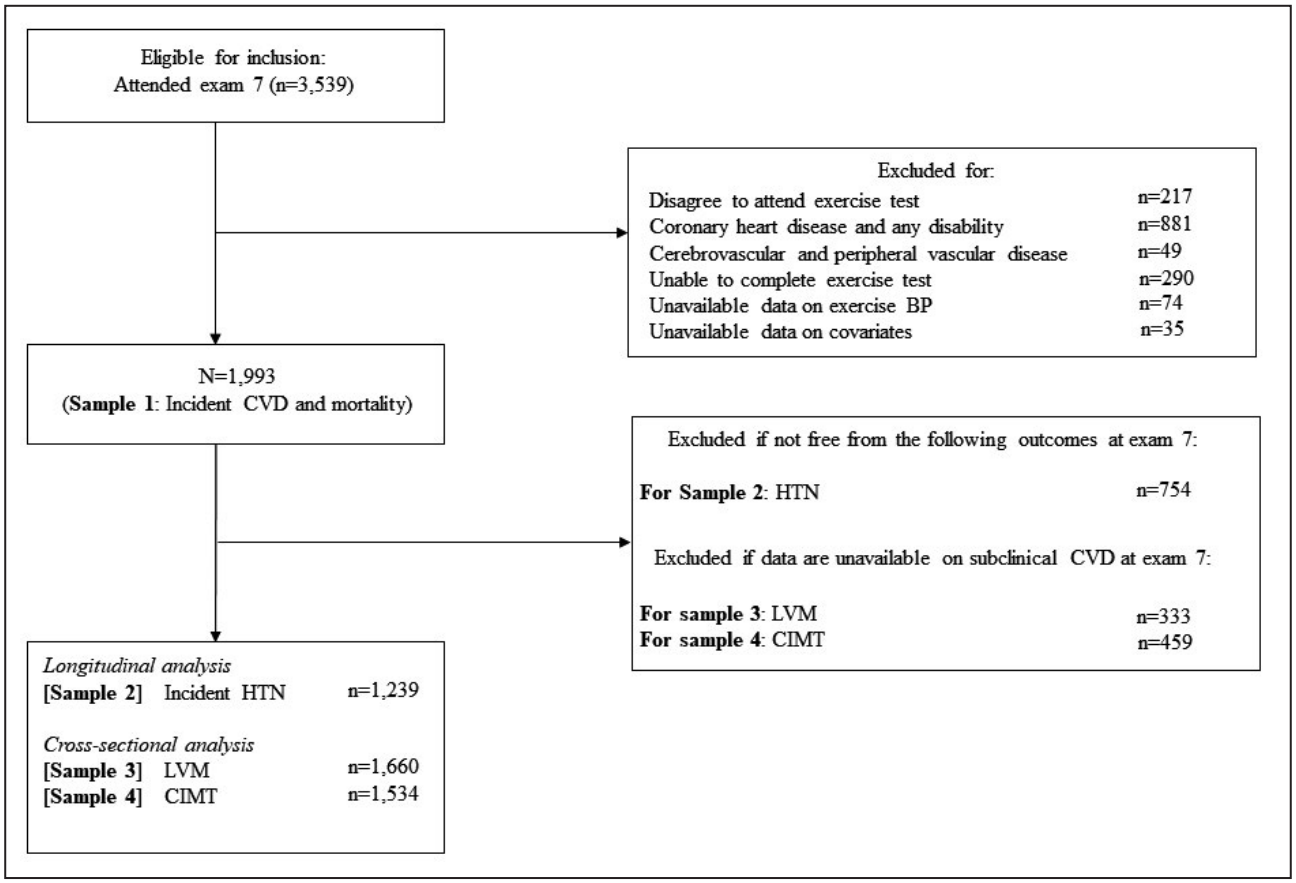

Figure. Consolidated Standards of Reporting Trials diagram of participant flow.
BP indicates blood pressure; CIMT, carotid intima-media thickness; CVD, cardiovascular disease; HTN, hypertension; and LVM, left ventricular mass.

Center institutional review board, and all participants provided written informed consent.

Submaximal Exercise Test

The submaximal exercise test was conducted using the Bruce protocol on a treadmill at examination cycle 7. In all participants, BP was obtained on the treadmill in a standing position before the start of the exercise test. Participants then completed 2 stages of the submaximal exercise test (6 minutes of Bruce protocol), each stage lasting 3 minutes. Exercise BP was recorded at the midpoint of the first (1.7 mph at 10% grade) and second (2.5 mph at 12% grade) stages of the submaximal exercise test. BP recovery after exercise was recorded at the end of each minute for 4 minutes of the recovery phase in a supine position. For the present investigation, the following exercise test variables were included: (1) *exercise SBP*, defined as SBP measured during the second stage of the submaximal exercise test; (2) *exercise DBP,* defined as DBP measured during the second stage of the submaximal exercise test; (3) *SBP recovery*, defined as exercise SBP minus SBP measured after 3 minutes of the submaximal exercise test; and (4) *DBP recovery*, defined as exercise DBP minus DBP measured after 3 minutes of the exercise test. As a secondary analysis, we created 4 new exercise BP variables: (1) *change in exercise SBP*, defined as exercise SBP minus preexercise standing SBP; (2) *change in exercise DBP*, defined as exercise DBP minus preexercise standing DBP; (3) *3 minutes postexercise SBP*, defined as SBP measured 3 minutes after exercise; and (4) *3 minutes postexercise DBP*, defined as DBP measured 3 minutes after exercise.

Subclinical CVD Indicators

FOS participants underwent measurements for indicators of subclinical CVD at their eighth examination cycle (2005–2008). Echocardiography was performed using a Sonos 5500 (Philips) ultrasound machine, where 2-dimensionally guided M-mode tracings were recorded digitally with a minimum of 3 frames for averaging LVM. LVM was calculated according to the American Society of Echocardiography guidelines, applying the method of Devereux et al[20] as below:

$$LVM = 0.8[1.04(\text{LV internal dimensions} + \text{septal wall thickness} + \text{posterior wall thickness})^3 - (\text{LV internal dimensions})^3] + 0.6g$$

All echocardiograms were evaluated by an experienced sonographer or cardiologist using a standardized reading protocol.

Carotid ultrasound was performed by a certified sonographer following a standard protocol using an ultrasound device equipped with a high-resolution linear-array transducer with color Doppler and Doppler spectral analyzer (model SSH140A; Toshiba America Medical Systems). The common carotid arteries were imaged with a 7.5-MHz transducer, and the carotid bulb and internal carotid arteries (ICA) were imaged using a 5-MHz transducer (3-dB point: 6.2 MHz).[21] CIMT measurements were made from gated diastolic images of the left and right carotid arteries at the level of the distal common carotid artery, the carotid artery bulb, and the proximal 2 cm of the ICA. The *z* score of the mean of the maximum common carotid artery intima-media thickness and ICA intima-media thickness were obtained and then both *z* scores were averaged to generate an overall CIMT *z* score.[22] Replicate readings (n=25) of mean maximum ICA and common carotid artery intima-media thickness by 2 independent interpreters showed intraclass correlation coefficients of 0.74 and 0.90, respectively.[23]

Outcomes of Interest

The incident outcomes of interest for this investigation are new-onset hypertension, CVD, and all-cause mortality. Information on all outcomes was obtained by medical history questionnaire, physical examination, hospitalization records, and communication with physicians. Hypertension was defined at each follow-up FOS examination as having an SBP/DBP ≥140/90 mm Hg or the use of antihypertensive medications after examination cycle 7.[24] CVD was defined as of the occurrence of new-onset coronary heart disease (fatal or nonfatal myocardial infarction, unstable angina [prolonged ischemic episode with documented reversible ST-segment changes]), peripheral vascular disease (intermittent claudication), cerebrovascular disease (ischemic or hemorrhagic stroke, or transient ischemic attack), or heart failure after examination cycle 7. Finally, all-cause mortality was defined as death attributable to any causes after examination cycle 7.

Covariates

At examination cycle 7, data on covariates were collected from routine medical history, physical examination, and laboratory assessment. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. Baseline BP represents a standing left arm BP obtained by the physician using a modified measurement protocol for standing participants before the exercise test. Peak heart rate (HR) was defined as HR measured during the second stage of the exercise test (2.5 mph at 12% grade). Hypertension was defined at each follow-up Framingham Heart Study examination as having a seated SBP/DBP ≥140/90 mm Hg or the use of antihypertensive medications. Diabetes mellitus was defined as a fasting glucose ≥126 mg/dL (≥7.0 mmol/L) or use of insulin or other hypoglycemic medications. Participants who reported smoking ≥1 cigarette/day during the year before examination cycle 7 were classified as current smokers using a self-questionnaire. Information on CVD was collected by a medical history questionnaire, physical examination, hospitalization records, and was adjudicated by a physician.

Statistical Analysis

In all analyses, exercise BP variables were standardized (Figure S1) and used as continuous variables in all models. LVM (log-transformed) and CIMT (mean *z* score of common carotid artery and ICA intima-media thickness) were included in the analysis as continuous variables.

We evaluated the cross-sectional associations between exercise BP variables (independent variables, separate model for each) and indicators of subclinical CVD (dependent variables, separate model for each) using linear regression models, adjusting for age, sex, standing preexercise SBP, standing preexercise DBP, resting HR, peak HR, current smoking status, BMI, total cholesterol (TC): high-density lipoprotein cholesterol (HDL-C) ratio (TC/HDL-C), diabetes mellitus, use of antihypertensive medication, and lipid-lowering medication.

Cox proportional hazards regression models with discrete time intervals were used to examine the longitudinal association between exercise BP variables and the incidence of hypertension, adjusting for age, sex, standing preexercise SBP, standing preexercise DBP, resting HR, peak HR, current smoking status, BMI, TC/HDL-C, diabetes mellitus, and use of lipid-lowering medication at examination cycle 7. Additionally, we explored the longitudinal relations of exercise BP variables with the incidence of CVD, and all-cause mortality using Cox proportional hazards regression models, adjusting for age, sex, standing preexercise SBP, standing preexercise DBP, resting HR, peak HR, current smoking status, BMI, TC/HDL-C, diabetes mellitus, and use of antihypertensive and lipid-lowering medication at baseline. Also, we

further adjusted for exercise SBP or DBP in models where SBP or DBP recovery was the exposure of interest. We conducted sensitivity analysis after excluding participants on any type of antihypertensive treatment to mitigate the impact of antihypertensive therapy on the associations of exercise BP variables with the presence of subclinical CVD or the incidence of CVD and all-cause mortality. As a secondary analysis, we related the new exercise BP variables (change in SBP, change in DBP, 3 minutes postexercise SBP, and 3 minutes postexercise DBP) to indicators of subclinical CVD and also to the incidence of hypertension, CVD, and all-cause mortality. Additionally, we examined the conjoint association of exercise BP variables with the outcomes. We confirmed that the proportional hazards assumption was met for each of the outcomes using visual inspection of Schoenfeld residuals and also by including an interaction term between log time and each exercise BP variable in the Cox regression models.

A 2-sided value of $P<0.05$ was considered statistically significant for all models. All analyses were performed using SAS software version 9.4 (SAS Institute Inc, Cary, NC).

RESULTS

The baseline characteristics of the participants (sample 1) are summarized in Table 1. Overall, the mean age at baseline was 58 years. The prevalence of overweight and obesity was 44.2% and 24.2% at baseline, respectively. Approximately 34% of participants had hypertension at baseline. Characteristics of participants excluded from this investigation (n=1546) are presented in Table S1.

Association Between BP Responses to Submaximal Exercise and Indicators of Subclinical CVD

The cross-sectional associations between BP responses to submaximal exercise and indicators of subclinical CVD are shown in Table 2. Overall, several statistically significant associations were noted. In multivariable-adjusted models, there was a positive association of exercise SBP with LVM and CIMT. We also observed direct relations between exercise DBP and LVM. SBP recovery was inversely associated with LVM and CIMT, whereas DBP recovery was inversely associated with CIMT only after adjustment for covariates. In sensitivity analysis after excluding participants on any type of antihypertensive treatment, the results were similar to the main analysis. All observed associations between exercise BP variables and indicators of subclinical CVD remained statistically significant (Table 2).

Table 1. Characteristics of the Largest Study Sample

	Men (n=933)	Women (n=1060)
Participants characteristics		
Age, y	58±9	58±8
Body mass index, kg/m^2	28.4±4.0	26.5±4.8
TC, mg/dL	198±34	208±36
HDL-C, mg/dL	47±13	63±17
LDL-C, mg/dL	125±30	121±34
Triglycerides, mg/dL	136±87	121±66
Lipid-lowering medication, n (%)	147 (15.8)	129 (12.2)
Fasting blood glucose, mg/dL	104±21	96±18
TC/HDL-C	4.5±1.3	3.5±1.1
Standing preexercise SBP, mm Hg	121±17	116±17
Standing preexercise DBP, mm Hg	77±11	73±11
Antihypertensive medication, n (%)	243 (26.0)	219 (20.7)
Resting HR, beats per min	62.5±10.1	65.7±9.8
Peak HR, beats per min	119.4±17.3	134.0±17.6
Smoking, n (%)	112 (12.0)	132 (12.5)
Exercise test variables		
Exercise SBP, mm Hg	168±24	162±25
Exercise DBP, mm Hg	77±14	73±15
SBP recovery, mm Hg	24±18	23±17
DBP recovery, mm Hg	−1±13	−3±13

Exercise SBP was defined as SBP measured during the second stage of the exercise test (2.5 mph at 12% grade); exercise DBP was defined as DBP measured during the second stage of the exercise test (2.5 mph at 12% grade); SBP recovery was defined as exercise SBP during the second stage minus SBP measured after 3 minutes of submaximal exercise test; DBP recovery was defined as exercise DBP during the second stage minus DBP measured after 3 minutes of submaximal exercise test. DBP indicates diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; HR, heart rate; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; and TC, total cholesterol. Values are mean±SD unless otherwise indicated.

Associations of BP Responses to Submaximal Exercise With the Incidence of Hypertension, CVD, and All-Cause Mortality

During 12 years of follow-up, 550 (44.4%) developed new-onset hypertension, 322 (16.2%) sustained a first CVD event, and 300 (15.1%) died. The longitudinal associations between exercise BP variables and the risk of hypertension, CVD, and all-cause mortality are presented in Table 3. Both higher exercise SBP and exercise DBP were associated with a greater risk of developing hypertension, adjusting for age, sex, standing preexercise SBP, standing preexercise DBP, resting HR, peak HR, current smoking

Table 2. Associations Between BP Responses to the Submaximal Exercise Test and Indicators of Subclinical CVD

	All Participants (n=1660)			Participants Not on Antihypertensive Treatment (n=1301)		
LV Mass	β Est.	SE	*P* Value	β Est.	SE	*P* Value
Exercise SBP	0.02	0.01	<0.001*	0.02	0.01	0.005*
Exercise DBP	0.01	0.01	0.004*	0.02	0.01	0.002*
SBP recovery	−0.03	0.01	<0.001*	−0.03	0.01	<0.001*
DBP recovery	0.005	0.01	0.53	−0.003	0.01	0.73
	All Participants (n=1534)			Participants Not on Antihypertensive Treatment (n=1185)		
CIMT	β Est.	SE	*P* Value	β Est.	SE	*P* Value
Exercise SBP	0.08	0.02	<0.001*	0.08	0.02	0.002*
Exercise DBP	0.006	0.02	0.73	0.01	0.02	0.58
SBP recovery	−0.07	0.02	0.003*	−0.08	0.03	0.002*
DBP recovery	−0.09	0.03	0.003*	−0.1	0.03	0.003*

Models were adjusted for age, sex, standing preexercise SBP, standing preexercise DBP, resting HR, current smoking status, body mass index, total cholesterol/high-density lipoprotein cholesterol, diabetes mellitus, use of antihypertensive medication, lipid-lowering medication, and peak heart rate at exam 7. Models using SBP recovery as exposure of interest were further adjusted for exercise SBP. Models using DBP recovery as exposure of interest were further adjusted for exercise DBP. Exercise SBP was defined as SBP measured during the second stage of the exercise test (2.5 mph at 12% grade). Exercise DBP was defined as DBP measured during the second stage of the exercise test (2.5 mph at 12% grade). SBP recovery was defined as exercise SBP during the second stage minus SBP measured after 3 minutes of submaximal exercise test. DBP recovery was defined as exercise DBP during the second stage minus DBP measured after 3 minutes of submaximal exercise test. Peak heart rate was defined as heart rate measured during the second stage of the exercise test (2.5 mph at 12% grade). All measures of the association were expressed per 1-SD increment in the exercise variable. SDs are equal to (1) LV mass (sample 3, n=1660): 25 mm Hg (exercise SBP), 14 mm Hg (exercise DBP), 17 mm Hg (SBP recovery), and 13 mm Hg (DBP recovery); and (2) CIMT (sample 4, n=1534): 24 mm Hg (exercise SBP), 14 mm Hg (exercise DBP), 18 mm Hg (SBP recovery), and 13 mm Hg (DBP recovery). BP indicates blood pressure; CIMT, carotid intima-media thickness; CVD, cardiovascular disease; DBP, diastolic blood pressure; LV, left ventricular; SBP, systolic blood pressure; and TC, total cholesterol.
*$P<0.05$.

status, BMI, TC/HDL-C, diabetes mellitus, and use of lipid-lowering medications. Higher exercise DBP was associated with an increased risk of CVD and all-cause mortality. Additionally, both SBP and DBP recovery were inversely associated with the risk of hypertension in multivariable-adjusted models. Furthermore, SBP recovery was inversely associated with the risk of CVD and all-cause mortality after adjusting for covariates. We observed similar results even after the exclusion of participants on any type of antihypertensive treatment. However, the associations of exercise DBP with the incidence of CVD and all-cause mortality were no longer statistically significant (Table 3). As a secondary analysis, we adjusted for resting BP instead of standing preexercise BP and found similar results in all models (data not shown).

Sensitivity Analysis

The associations of the new exercise BP variables (change in SBP, change in DBP, 3 minutes postexercise SBP, and 3 minutes postexercise DBP) with indicators of subclinical CVD, incidence of hypertension, CVD, and all-cause mortality were similar to the main analysis (Tables S2 and S3). Compared with the individual models, we observed similar patterns of association when all exercise BP variables were modeled conjointly (Tables S4 and S5).

DISCUSSION

Principal Findings

In the current investigation, we observed several important findings. First, exercise BP variables measured in midlife were associated with indicators of subclinical CVD. Additionally, SBP and DBP during submaximal exercise, and SBP and DBP during recovery after submaximal exercise were strongly associated with the risk of developing hypertension after adjustment for potential confounders. Exercise DBP was also positively associated with the risk of CVD. Finally, SBP recovery was inversely associated with the risk of CVD and all-cause mortality in multivariable-adjusted models.

Comparison With the Literature

The Association of BP Responses to Submaximal Exercise With Subclinical CVD

Consistent with the present investigation, numerous studies have reported the positive associations of exercise SBP with LVM in middle-aged adults[13,14] and CIMT in middle-aged men.[15] We extend the findings in the literature in several ways. We observed that a higher exercise DBP during submaximal exercise and delayed SBP recovery after submaximal exercise in midlife (mean age, ≈60 years) were associated with higher LVM. Moreover, we observed the inverse association of SBP

Table 3. Associations Between BP Responses to the Submaximal Exercise Test and Incidence of Hypertension, CVD, and All-Cause Mortality

	All Participants (Number of Cases/Number at Risk=550/1239)		Participants Not on Antihypertensive Treatment	
Hypertension	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value
Exercise SBP	1.40 (1.20–1.62)	<0.001*	···	···
Exercise DBP	1.24 (1.10–1.40)	<0.001*	···	···
SBP recovery	0.46 (0.38–0.54)	<0.001*	···	···
DBP recovery	0.55 (0.45–0.67)	<0.001*	···	···
	All Participants (Number of Cases/Number at Risk=322/1993)		Participants Not on Antihypertensive Treatment (Number of Cases/Number at Risk=217/1531)	
CVD	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value
Exercise SBP	1.05 (0.90–1.22)	0.57	1.02 (0.85–1.23)	0.84
Exercise DBP	1.15 (1.02–1.30)	0.02*	1.12 (0.96–1.29)	0.14
SBP recovery	0.80 (0.69–0.93)	0.003*	0.83 (0.69–0.99)	0.04*
DBP recovery	0.94 (0.77–1.15)	0.54	0.96 (0.75–1.23)	0.73
	All Participants (Number of Cases/Number at Risk=300/1993)		Participants Not on Antihypertensive Treatment (Number of Cases/Number at Risk=210/1531)	
All-Cause Mortality	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value
Exercise SBP	1.05 (0.89–1.23)	0.58	0.97 (0.81–1.17)	0.77
Exercise DBP	1.13 (1.00–1.28)	0.05*	1.09 (0.94–1.27)	0.26
SBP recovery	0.76 (0.65–0.88)	<0.001*	0.78 (0.65–0.94)	0.008*
DBP recovery	0.96 (0.78–1.18)	0.70	1.01 (0.78–1.29)	0.96

Models were adjusted for age, sex, standing preexercise SBP, standing preexercise DBP, resting heart rate, current smoking status, body mass index, total cholesterol/high-density lipoprotein cholesterol, diabetes mellitus, use of antihypertensive, use of lipid-lowering medication, and peak heart rate at exam 7. Models using SBP recovery as exposure of interest were further adjusted for exercise SBP. Models using DBP recovery as exposure of interest were further adjusted for exercise DBP. Exercise SBP was defined as SBP measured during the second stage of the exercise test (2.5 mph at 12% grade). Exercise DBP was defined as DBP measured during the second stage of the exercise test (2.5 mph at 12% grade). SBP recovery was defined as exercise SBP during the second stage minus SBP measured after 3 minutes of submaximal exercise test in a supine position. DBP recovery was defined as exercise DBP during the second stage minus DBP measured after 3 minutes of submaximal exercise test in a supine. Peak heart rate was defined as heart rate measured during the second stage of the exercise test (2.5 mph at 12% grade). No results were reported regarding the relation between exercise BP variables and incident hypertension among participants not on antihypertensive treatment because they were already excluded from the original analysis. All measures of the association were expressed per 1-SD increment in the exercise variable. SDs are equal to: (1) hypertension (sample 2, n=1239): 23 mm Hg (exercise SBP), 14 mm Hg (exercise DBP), 17 mm Hg (SBP recovery), and 13 mm Hg (DBP recovery); and (2) CVD and all-cause mortality (sample 1, n=1993): 25 mm Hg (exercise SBP), 15 mm Hg (exercise DBP), 18 mm Hg (SBP recovery), and 13 mm Hg (DBP recovery). BP indicates blood pressure; CVD, cardiovascular disease; DBP, diastolic blood pressure; and SBP, systolic blood pressure.

*$P<0.05$.

recovery and DBP recovery after submaximal exercise with CIMT in our sample. These findings suggest the additional prognostic value of midlife exercise DBP and of BP recovery in relation to subclinical CVD outcomes in an overall healthier community-based sample.

Association of BP Responses to Exercise With the Risk of Hypertension

Investigators have reported on the association between BP responses to exercise in young adults and incident hypertension,[4–6] and they observed fairly consistent findings where higher SBP response to exercise was associated with a higher risk of developing hypertension, prospectively. However, a prospective cohort study investigating young adults in FOS participants noted that exaggerated DBP, but not SBP, during submaximal exercise was associated with a higher risk of hypertension.[1] The authors also reported that impaired SBP recovery after submaximal exercise was associated with higher incident hypertension.[1] The differences in findings across studies may be attributable to the use of different exercise test protocol (maximal versus submaximal), and varying age distributions of the study samples evaluated (middle-aged men versus young adults ([men and women]).

We observed that higher exercise SBP and DBP during submaximal exercise and delayed SBP and DBP recovery after submaximal exercise in midlife were associated with a greater risk of developing hypertension. The reason that we observed stronger associations compared with prior studies may be physiological impairments related to the abnormal BP responses to exercise usually observed with aging. Daida et al reported

that BP responses during exercise are accentuated with increasing age in normotensive individuals[25]. Moreover, it has been reported that endothelial function is impaired with aging due primarily to oxidative stress and inflammation even in the absence of chronic disease.[26] Collins et al[27] also noted that sympathetic and parasympathetic responses to exercise are significantly impaired with aging. However, the mechanisms underlying the age-specific association of BP responses to exercise with the risk of hypertension warrant further study.

Associations of BP Responses to Exercise With the Incidence of CVD and All-Cause Mortality

In accordance with the current investigation, prior studies documented that delayed SBP recovery after the maximal exercise test is associated with a higher risk of coronary heart disease in middle-aged men.[12,28] We confirmed the findings from prior studies using a submaximal treadmill test.

However, inconsistent with prior studies, we did not observe an association between exercise SBP during submaximal exercise in midlife and incidence of CVD after adjusting for potential confounders. Given that most prior studies investigated the association in middle-aged men using the maximal exercise test, different findings may be explained by the different characteristics of study participants (middle-aged men or young or middle-aged men and women versus middle-aged or older adults) and the exercise test protocol used (maximal versus submaximal stress test). Interestingly, Lewis et al[8] reported significant associations of exercise DBP and DBP recovery with the risk of CVD in young adults using FOS participants attending an earlier examination cycle (examination cycle 2 [1979–1983]; mean age, 43 years). In that study, the investigators reported an interaction between DBP response to submaximal exercise and age suggesting a greater prognostic utility of exercise DBP responses in young adults.[8] Thus, prognostic values of DBP response to submaximal exercise in midlife may be attenuated relative to similar measurements made in younger individuals.

Although evidence indicates that exercise SBP is positively associated with the risk of cardiovascular death[10,11] and all-cause mortality,[29] little is known regarding the associations of SBP recovery and all-cause mortality. A prospective cohort study reported that impaired SBP recovery after the maximal exercise test was not associated with all-cause mortality in middle-aged adults.[23] The different findings observed between this study and our investigation may be attributable to the use of different definition for SBP recovery (the ratio of SBP after 3 minutes of maximal exercise to peak exercise SBP versus SBP during the second stage of the submaximal exercise test minus SBP measured after 3 minutes of the submaximal exercise test), the use of a different exercise test protocol (maximal versus submaximal exercise tests), different characteristics of study participants (proportion of women; 24.0 versus 53.7%), and also a different follow-up period (6 years versus 12 years). However, Cole et al[30] reported that impaired HR recovery after exercise was associated with a higher risk of all-cause mortality. Given that both delayed HR and BP recovery after exercise are affected by impaired responses of the autonomic nervous system,[31] our findings of an inverse relation of SBP recovery after 3 minutes of submaximal exercise and all-cause mortality may be explained by the possibility that delayed SBP recovery may reflect an overactivity of the sympathetic nervous system and attenuated vagal reactivation.

Strengths and Limitations

There are several strengths of the present investigation. One particular strength is the use of a large sample comprised of community-based participants (n=1993), which reduces selection bias. Additionally, residual confounding is minimized by using a well-characterized sample with a comprehensive and detailed assessment of CVD risk factors. The submaximal exercise test allows for more precise and reliable exercise BP measurements[1] and may be of particular value in midlife when some individuals may be unable to sustain vigorous exercise.[32] In the current investigation, all participants simultaneously completed the exercise test at relatively low intensity (2.5 mph at 12% grade), thereby eliminating the confounding effects of cardiorespiratory fitness, which is usually observed in highly trained individuals because of increased cardiac output during maximal exercise.[33,34] There are limitations to be acknowledged in the present investigation. Other investigators have reported that the variability in exercise BP response may be of prognostic importance.[35] However, we were not able to examine the variability in exercise BP responses in relation to the risk of outcomes because of the unavailability of these data. FOS is comprised predominantly of white individuals of European ancestry, which limits the generalizability of our findings. Thus, the observed associations between BP responses to submaximal exercise in midlife and risk of future CVD outcomes need to be confirmed in multiethnic cohorts.

CONCLUSIONS

Higher submaximal exercise BP and impaired BP recovery after submaximal exercise in midlife may be markers of subclinical and clinical CVD and mortality in later life.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Materials

Tables S1–S5
Figure S1

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SUPPLEMENTAL MATERIAL

Table S1. Characteristics of participants included and excluded from the analysis.

	Included (n=1,993)	Excluded (n=1,546)
Age (years)	58±8	66±9
Body Mass Index (kg/m^2)	27.4±4.5	29.3±6.2
Total cholesterol (mg/dL)	203±35	196±38
HDL-C (mg/dL)	55±17	51±17
LDL-C (mg/dL)	123±32	115±33
Use of lipid-lowering medications (n, %)	276 (13.9)	166 (30.2)
SBP (mm Hg)	123±16	133±21
DBP (mm Hg)	75±9	73±11
Hypertension (n, %)	670 (33.6)	964 (62.8)
Use of antihypertensive medications (n, %)	462 (23.2)	756 (49.2)
Fasting glucose (mg/dL)	100±20	111±33
Diabetes (n, %)	126 (6.3)	269 (19.9)
Current Smoking (n, %)	244 (12.2)	239 (15.5)

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table S2. Associations between secondary exercise BP variables and indicators of subclinical CVD.

	All participants (n=1,660)			**Participants not on antihypertensive treatment (n=1,301)**		
LV mass	β Est.	SE	P value	β Est.	SE	P value
Change in exercise SBP	0.02	0.005	**<.001**	0.02	0.006	**.005**
Change in exercise DBP	0.01	0.005	**.003**	0.02	0.005	**.002**
3 minutes post-exercise SBP	0.03	0.007	**<.001**	0.03	0.008	**<.001**
3 minutes post-exercise DBP	-0.004	0.006	.55	0.002	0.007	.73
	All participants (n=1,534)			**Participants not on antihypertensive treatment (n=1,185)**		
CIMT	β Est.	SE	P value	β Est.	SE	P value
Change in exercise SBP	0.07	0.02	**<.001**	0.06	0.02	**.002**
Change in exercise DBP	0.008	0.02	.65	0.01	0.02	.58
3 minutes post-exercise SBP	0.11	0.03	**<.001**	0.09	0.03	**.002**
3 minutes post-exercise DBP	0.07	0.02	**<.001**	0.07	0.02	**.003**

BP, blood pressure; CVD, cardiovascular disease; LV, left ventricular; Est., estimate; SE, standard error; SBP, systolic blood pressure; DBP, diastolic blood pressure; CIMT, carotid intima-media thickness.

Model was adjusted for age, sex, standing pre-exercise SBP, standing pre-exercise DBP, resting heart rate, current smoking status, BMI, TC/HDL-C, diabetes, use of antihypertensive medication, lipid-lowering medication, and peak heart rate at exam 7; Models using 3 minutes post-exercise SBP as an exposure of interest were further adjusted for exercise SBP; Models using 3 minutes post-exercise DBP as an exposure of interest were further adjusted for exercise DBP; Change in exercise SBP was defined as SBP measured during the second stage of the exercise test (2.5 mph at 12% grade) minus pre-exercise standing SBP; Change in exercise DBP was defined as DBP measured during the second stage of the exercise test (2.5 mph at 12% grade) minus pre-exercise standing DBP; 3 minutes post-exercise SBP was defined as SBP measured 3 minutes after exercise; 3 minutes post-exercise DBP was defined as DBP measured 3 minutes after exercise; Peak HR was defined as HR measured during the second stage of the exercise test (2.5 mph at 12% grade); All measures of the association were expressed per 1 standard deviation increment in the

exercise variable. Standard deviations are equal to: (1) LV mass (**Sample 3**, n=1,660): 19 mmHg (Change in exercise SBP), 14 mmHg (Change in exercise DBP), 20 mmHg (3 minutes post-exercise SBP), and 9 mmHg (3 minutes post-exercise DBP), and (2) CIMT (**Sample 4**, n=1,534): 19 mmHg (Change in exercise SBP), 14 mmHg (Change in exercise DBP), 20 mmHg (3 minutes post-exercise SBP), and 9 mmHg (3 minutes post-exercise DBP).

Table S3. Associations of secondary exercise BP variables with the incidence of hypertension, CVD and all-cause mortality.

	All participants (#cases/#at risk=554/1,240)		**Participants not on antihypertensive treatment**	
Hypertension	HR (95% CI)	P value	HR (95% CI)	P value
Change in exercise SBP	1.32 (1.17-1.49)	**<.001**	--	--
Change in exercise DBP	1.23 (1.10-1.39)	**<.001**	--	--
3 minutes post-exercise SBP	2.19 (1.84-2.60)	**<.001**	--	--
3 minutes post-exercise DBP	1.51 (1.31-1.74)	**<.001**	--	--
	All participants (#cases/#at risk=322/1,993)		**Participants not on antihypertensive treatment (#cases/#at risk=217/1,531)**	
CVD	HR (95% CI)	P value	HR (95% CI)	P value
Change in exercise SBP	1.04 (0.92-1.17)	.54	1.02 (0.88-1.17)	.84
Change in exercise DBP	1.15 (1.02-1.29)	**.02**	1.11 (0.97-1.28)	.14
3 minutes post-exercise SBP	1.30 (1.10-1.53)	**.002**	1.22 (1.01-1.48)	**.04**
3 minutes post-exercise DBP	1.05 (0.91-1.21)	.54	1.03 (0.87-1.23)	.73
	All participants (#cases/#at risk=300/1,993)		**Participants not on antihypertensive treatment (#cases/at risk=210/1,531)**	
All-cause mortality	HR (95% CI)	P value	HR (95% CI)	P value
Change in exercise SBP	1.03 (0.91-1.17)	.60	0.98 (0.85-1.13)	.77
Change in exercise DBP	1.13 (1.00-1.28)	**.05**	1.09 (0.94-1.26)	.26
3 minutes post-exercise SBP	1.35 (1.14-1.60)	**<.001**	1.31 (1.07-1.59)	**.008**
3 minutes post-exercise DBP	1.03 (0.90-1.19)	.71	1.00 (0.83-1.19)	.96

BP, blood pressure; CVD, cardiovascular disease; HR, hazards ratio; CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure. Models were adjusted for age, sex, standing pre-exercise SBP, standing pre-exercise DBP, resting heart

rate, current smoking status, BMI, TC/HDL-C, diabetes, fasting blood glucose, use of antihypertensive medication, lipid-lowering medication, and peak heart rate; Change in exercise SBP was defined as SBP measured during the second stage of the exercise test (2.5 mph at 12% grade) minus pre-exercise standing SBP; Change in exercise DBP was defined as DBP measured during the second stage of the exercise test (2.5 mph at 12% grade) minus pre-exercise standing DBP; 3 minutes post-exercise SBP was defined as SBP measured 3 minutes after exercise; 3 minutes post-exercise DBP was defined as DBP measured 3 minutes after exercise; Peak heart rate was defined as heart rate measured during the second stage of the exercise test (2.5 mph at 12% grade); No results were reported regarding the relation between new exercise BP variables and incident hypertension among participants not on antihypertensive treatment because they were already excluded from the original analysis; All measures of the association were expressed per 1 standard deviation increment in the exercise variable; Standard deviations are equal to: (1) Hypertension (**Sample 2**, n=1,239): 19 mmHg (Change in exercise SBP), 13 mmHg (Change in exercise DBP), 17 mmHg (3 minutes post-exercise SBP), and 9 mmHg (3 minutes post-exercise DBP), and (2) CVD and all-cause mortality (**Sample 1**, n=1,993): 19 mmHg (Change in exercise SBP), 14 mmHg (Change in exercise DBP), 20 mmHg (3 minutes post-exercise SBP), and 9 mmHg (3 minutes post-exercise DBP).

Table S4. Conjoint association of exercise BP variables with indicators of subclinical CVD.

	All participants (n=1,660)			Participants not on antihypertensive treatment (n=1,301)		
LV mass	β est.	SE	P value	β est.	SE	P value
Exercise SBP	0.05	0.01	**<.001**	0.05	0.01	**<.001**
Exercise DBP	-0.002	0.01	.82	0.008	0.01	.43
SBP recovery	-0.03	0.01	**<.001**	-0.03	0.01	**<.001**
DBP recovery	0.01	0.01	.10	0.006	0.01	.54
	All participants (n=1,534)			Participants not on antihypertensive treatment (n=1,185)		
CIMT	β. Est.	SE	P value	β. Est.	SE	P value
Exercise SBP	0.14	0.03	**<.001**	0.15	0.04	**<.001**
Exercise DBP	0.06	0.03	.06	0.07	0.04	**.05**
SBP recovery	-0.06	0.02	**.02**	-0.07	0.03	**.02**
DBP recovery	-0.07	0.03	**.02**	-0.08	0.03	**.02**

BP, blood pressure; CVD, cardiovascular disease; LV, left ventricular; SE, standard error; SBP, systolic blood pressure; DBP, diastolic blood pressure; CIMT, carotid intima-media thickness; VIF, variance inflation factor. Models were adjusted for age, sex, standing pre-exercise SBP, standing pre-exercise DBP, resting HR, current smoking status, BMI, TC/HDL-C, diabetes, use of antihypertensive medication, lipid-lowering medication, and peak heart rate at exam 7; Exercise SBP was defined as SBP measured during the second stage of the exercise test (2.5 mph at 12% grade); Exercise DBP was defined as DBP measured during the second stage of the exercise test (2.5 mph at 12% grade); SBP recovery was defined as Exercise SBP during the second stage minus SBP measured after three minutes of submaximal exercise test; DBP recovery was defined as Exercise DBP during the second stage minus DBP measured after three minutes of submaximal exercise test; Peak heart rate was defined as heart rate measured during the second stage of the exercise test (2.5 mph at 12% grade); Variation inflation factors (VIFs) were 4.61 (exercise SBP), 4.51 (exercise DBP), 2.31 (SBP recovery), and 3.64 (DBP recovery) in the model evaluating the association between exercise BP variables and LV mass; VIFs were 4.56 (exercise SBP), 4.60 (exercise DBP), 2.35 (SBP recovery), and 3.77 (DBP recovery) in the model

evaluating the association between exercise BP variables and CIMT; All measures of the association were expressed per 1 standard deviation increment in the exercise variable.

Table S5. Conjoint association of exercise BP variables with the incidence of hypertension, CVD, and all-cause mortality.

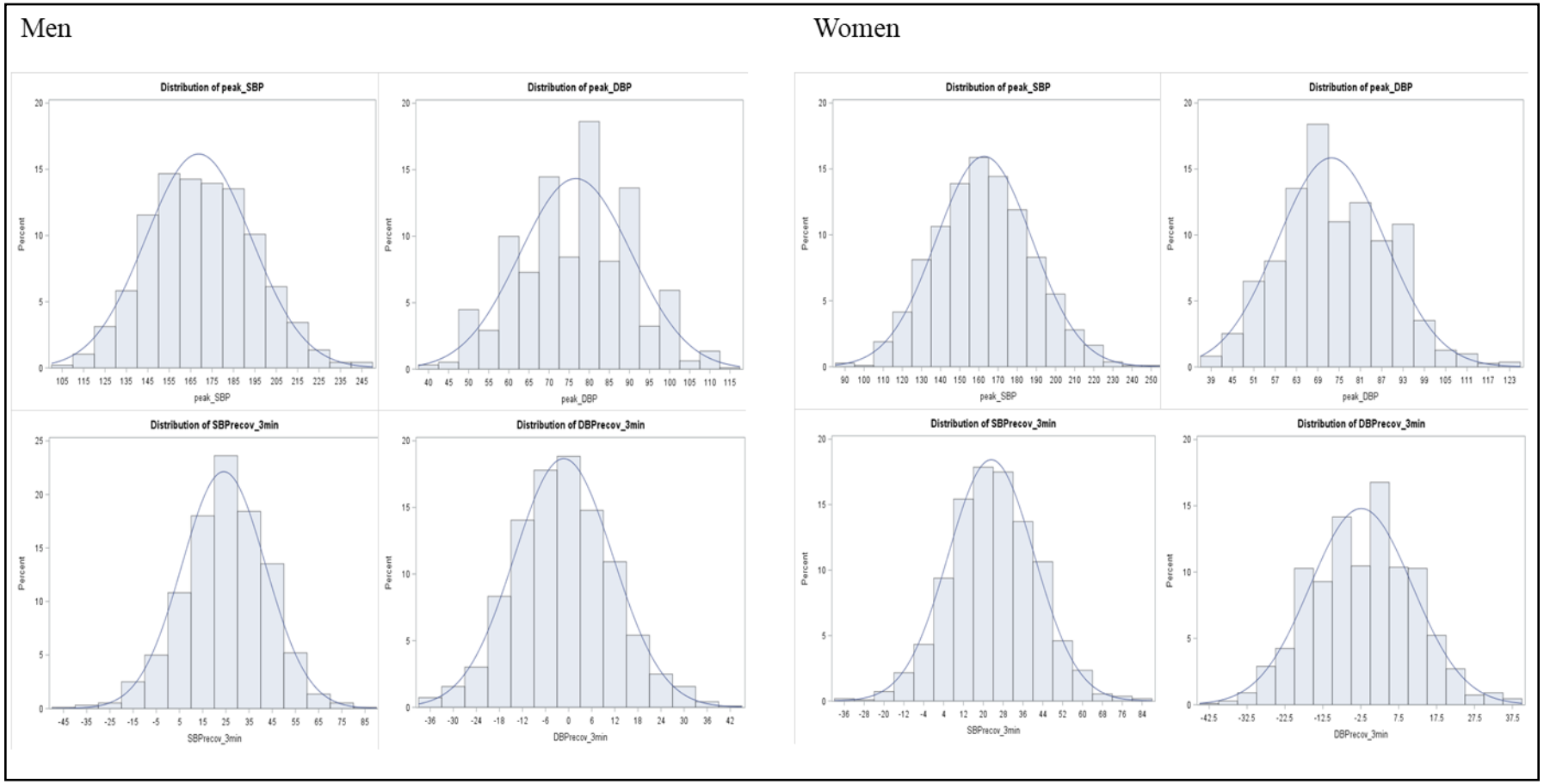
	All participants (#cases/#at risk=550/1,239)		**Participants not on antihypertensive treatment**	
Hypertension	HR (95% CI)	P value	HR (95% CI)	P value
Exercise SBP	2.72 (2.15-3.45)	**<.001**	--	--
Exercise DBP	1.72 (1.36-2.16)	**<.001**	--	--
SBP recovery	0.50 (0.46-0.60)	**<.001**	--	--
DBP recovery	0.67 (0.54-0.83)	**<.001**	--	--
	All participants (#cases/#at risk=322/1,993)		**Participants not on antihypertensive treatment (#cases/#at risk=217/1,531)**	
CVD	HR (95% CI)	P value	HR (95% CI)	P value
Exercise SBP	1.27 (1.02-1.58)	**.03**	1.27 (1.03-1.57)	**.03**
Exercise DBP	1.14 (0.91-1.42)	.25	1.14 (0.91-1.42)	.25
SBP recovery	0.81 (0.70-0.95)	**.01**	0.81 (0.70-0.94)	**.006**
DBP recovery	0.99 (0.81-1.22)	.92	0.99 (0.81-1.22)	.92
	All participants (#cases/#at risk=300/1,993)		**Participants not on antihypertensive treatment (#cases/#at risk=210/1,531)**	
All-cause mortality	HR (95% CI)	P value	HR (95% CI)	P value
Exercise SBP	1.34 (1.08-1.67)	**.008**	1.23 (0.95-1.60)	.12
Exercise DBP	1.08 (0.86-1.36)	.49	1.02 (0.77-1.35)	.90
SBP recovery	0.76 (0.65-0.89)	**<.001**	0.77 (0.64-0.94)	**.008**

DBP recovery	1.02 (0.83-1.26)	.83	1.07 (0.82-1.38)	.63

BP, blood pressure; CVD, cardiovascular disease; HR, hazard ratio; CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; VIF, variance inflation factor.

Models were adjusted for age, sex standing pre-exercise SBP, standing pre-exercise DBP, resting HR, current smoking status, BMI, TC/HDL-C, diabetes, use of antihypertensive, use of lipid-lowering medication, and peak heart rate at exam 7; Exercise SBP was defined as SBP measured during the second stage of the exercise test (2.5 mph at 12% grade); Exercise DBP was defined as DBP measured during the second stage of the exercise test (2.5 mph at 12% grade); SBP recovery was defined as Exercise SBP during the second stage minus SBP measured after three minutes of submaximal exercise test in a supine position; DBP recovery was defined as Exercise DBP during the second stage minus DBP measured after three minutes of submaximal exercise test in a supine; Peak heart rate was defined as heart rate measured during the second stage of the exercise test (2.5 mph at 12% grade); No results were reported regarding the relation between exercise BP variables and incident hypertension among participants not on antihypertensive treatment because they were already excluded from the original analysis; Variance inflation factors (VIFs) were 4.35 (exercise SBP), 4.42 (exercise DBP), 2.51 (SBP recovery), and 3.66 (DBP recovery) in the model evaluating the association between exercise BP variables and incidence of hypertension; VIFs were 4.47 (exercise SBP), 4.53 (exercise DBP), 2.33 (SBP recovery), and 3.70 (DBP recovery) in the model evaluating the association between exercise BP variables and incidence of CVD and all-cause mortality; All measures of the association were expressed per 1 standard deviation increment in the exercise variable.

Figure S1. **Distribution of exercise blood pressure variables.**



SBP, systolic blood pressure; DBP diastolic blood pressure

Peak SBP was defined as SBP measured during the second stage of the exercise test (2.5 mph at 12% grade); Peak DBP was defined as DBP measured during the second stage of the exercise test (2.5 mph at 12% grade); SBPrecov_3min was defined as Exercise SBP during the second stage minus SBP measured after three minutes of submaximal exercise test; DBPrecov_3min was defined as Exercise DBP during the second stage minus DBP measured after three minutes of submaximal exercise test.