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| Citation       | Spartano, Nicole L., Asya Lyass, Martin G. Larson, Gregory D. Lewis, and Ramachandran S. Vasan. 2016. “Submaximal Exercise Systolic Blood Pressure and Heart Rate at 20 Years of Follow-up: Correlates in the Framingham Heart Study.” Journal of the American Heart Association: Cardiovascular and Cerebrovascular Disease 5 (6): e002821. doi:10.1161/JAHA.115.002821. http://dx.doi.org/10.1161/JAHA.115.002821. |
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| Published Version | doi:10.1161/JAHA.115.002821                                                                                                                                                                                                                                                                                                                                                               |
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Submaximal Exercise Systolic Blood Pressure and Heart Rate at 20 Years of Follow-up: Correlates in the Framingham Heart Study

Nicole L. Spartano, PhD; Asya Lyass, PhD; Martin G. Larson, ScD; Gregory D. Lewis, MD; Ramachandran S. Vasan, MD

**Background**—Beyond their resting values, exercise responses in blood pressure (BP) and heart rate (HR) may add prognostic information for cardiovascular disease (CVD). In cross-sectional studies, exercise BP and HR responses correlate with CVD risk factors; however, it is unclear which factors influence longitudinal changes in exercise responses over time, which is important for our understanding of the development of CVD.

**Methods and Results**—We assessed BP and HR responses to low-level exercise tests (6-minute Bruce protocol) in 1231 Framingham Offspring participants (55% women) who underwent a routine treadmill test in 1979–1983 (baseline; mean age 39±8 years) that was repeated in 1998–2001 (follow-up; mean age 58±8 years). Adjusting for baseline exercise responses, we related the follow-up exercise responses to baseline CVD risk factors and to their changes between examinations. Compared with men, women had greater rise in exercise systolic (S)BP and HR at 20-year follow-up (both \(P<0.005\)). Baseline blood lipid levels, resting SBP and HR, and smoking status were associated with greater exercise SBP at follow-up (all \(P<0.05\)). Weight gain across examinations was associated with higher exercise SBP and HR at follow-up (both \(P=0.0001\)). Smoking cessation was associated with a 53% reduced risk of attaining the highest quartile of exercise SBP (≥180 mm Hg) at follow-up (\(P<0.05\)).

**Conclusion**—An adverse CVD risk factor profile in young adults and its worsening over time were associated with higher SBP and HR responses to low-level exercise in midlife. Maintaining or adopting a healthy risk factor profile may favorably impact the exercise responses over time. ([J Am Heart Assoc. 2016;5:e002821 doi: 10.1161/JAHA.115.002821])

**Key Words:** aging • blood pressure • epidemiology • exercise • heart rate • risk factors

**E**xaggerated systolic blood pressure (SBP) response to exercise is a risk factor for the future development of hypertension\(^1\)–\(^3\) and left ventricular hypertrophy (LVH)\(^4\) and has been associated with greater cardiovascular disease (CVD) mortality.\(^5\)–\(^7\) During exercise, SBP rises as a result of increasing heart rate (HR) and stroke volume at a higher rate than the proportional increase in vascular compliance.\(^8\) However, physiological changes in older age cause either elevation or decline in the HR and SBP responses to exercise, through several mechanisms including reduced physical fitness, increased vascular stiffness, impaired baroreceptor sensitivity, and chronotropic incompetence.\(^9\)–\(^14\) Traditional modifiable risk factors also play an important role in determining the cardiovascular response to exercise. In this context, factors that determine the evolution of exercise SBP and HR responses over time and with age have not been evaluated in a longitudinal study.

Elevated resting SBP is associated generally with exaggerated SBP during exercise,\(^9\) but the patterns of resting and exercise SBP over time can also diverge. For instance, it is conceivable that an individual with a stable clinical measure of resting SBP across 2 decades may demonstrate a substantial increase in exercise SBP during that same time period. Understanding factors that influence baseline exercise SBP and HR responses is critical to our appreciation of how these same or additional factors may also influence the evolution of exercise responses over time in individuals. Such knowledge may inform us about strategies to prevent age-related increases in exercise responses and their prognostic implications. In the present investigation, we examined the SBP and HR responses...
during a submaximal exercise test at 2 time points (2 decades apart) in a large community-based sample.

The use of submaximal exercise responses was preferred for this investigation (instead of responses to maximal test) to avoid issues of differing workload for individuals reaching different levels of the exercise test. The purpose of this investigation was to determine how changes in CVD risk factors influence the evolution of exercise SBP and HR responses in adults at baseline and during a 2-decade period of observation. We hypothesized that greater burden of risk factors in midlife and an increase in levels of these risk factors across midlife would be associated with an increased exercise SBP and HR response at follow-up in later life. Results from this study will help us understand the factors affecting change in exercise responses over time and provide insights into key factors that could be potentially modified to maintain an optimal exercise response over the life course, defined strictly in this study as remaining in the lowest 3 quartiles of exercise SBP (≤180 mm Hg) at follow-up, a level consistent with a lower risk for CVD. An optimal exercise response was also defined broadly as preventing large increases in exercise HR or SBP over time.

Methods
In 1948, enrollment began for the Framingham Heart Study (FHS), a prospective epidemiological study of CVD. Between 1979 and 1983, 3333 participants from the second generation (the Framingham Offspring Study, composed of the children of the original cohort, and their spouses) completed stage 2 of the baseline exercise treadmill test (ETT) at the FHS. About 20 years later (1998–2001), 1730 participants repeated the ETT (completing stage 2) at a follow-up FHS examination. We excluded people if they had prevalent CVD (myocardial infarction, angina, stroke/transient ischemic attack, peripheral vascular disease, and congestive heart failure, n=43) or diabetes mellitus (DM) (defined as fasting glucose ≥126 mg/dL or taking diabetes medications, n=5) or used lipid-lowering medications (n=8), at baseline only. We also excluded people who used β-blockers (n=158) or antihypertension medications (n=285) at baseline or follow-up. After exclusions, there remained 1231 subjects (55% women) who underwent serial ETT. The Institutional Review Board at the Boston University Medical Center approved the study protocols, and all participants gave written informed consent.

Exercise Treadmill Test
The baseline ETT occurred when most participants were adults (mean age 39 years, only 7 participants were <20 years) by using the Bruce protocol. After a brief warmup, participants completed at least 2 stages of ETT, with each stage lasting 3 minutes: stage 1 (1.7 mph, 10% grade) and stage 2 (2.5 mph, 12% grade). The baseline ETT continued after stage 2, but none of the measurements beyond stage 2 were used in the current investigation. In total, 2.5% of participants who undertook the ETT at baseline were excluded because they did not complete stage 2 of the ETT. The follow-up ETT (mean age 58 years) was performed by using the same protocol as the first ETT, with the exception that it was terminated after completion of stage 2. At follow-up, 8% of participants were excluded for not completing stage 2 of the ETT. At baseline and follow-up, BP and HR were measured at rest (before exercise onset) and midway through stage 2 of ETT. Hereafter, stage 2 SBP and HR will be referred to as “exercise SBP” and “exercise HR.”

Assessment of Traditional CVD Risk Factors
Risk factors and other covariates were measured during the FHS visit on the same day as each ETT. The following covariates and the change in these covariates across the 2 examinations (cycles 2 and 7) were included in our analysis: age, sex, smoking status (defined as smoking cigarettes regularly in the year preceding the FHS examination), SBP, diastolic blood pressure (DBP), and HR at rest, body mass index (BMI), total cholesterol (TC)/high-density lipoprotein (HDL), DM, lipid-lowering treatments.

Statistical Analysis
We present descriptive statistics as means and standard deviations for continuous variables and as counts and percentages for categorical variables. We used t and χ² tests to determine whether there were differences among demographic variables. We used multiple linear regression to predict exercise SBP and HR responses in cross-sectional data, at the baseline and at the follow-up examinations using risk factors from the corresponding examination.

We calculated changes in risk factors (follow-up minus baseline) for continuous variables and change in status across the 2 examinations for categorical variables. We used multiple linear regression to predict exercise SBP and HR (dependent variables) at follow-up with baseline ETT variables, baseline risk factors, and interim change in risk factors. Baseline physical activity index was not associated with exercise SBP or HR at follow-up in multivariable models (data not shown) and therefore was removed from all models. We also used multiple logistic regression to predict being in the highest quartile of exercise SBP at follow-up (≥180 mm Hg) by using baseline ETT variables, baseline risk factors, and interim change in risk factors. We did not evaluate predictors of
Correlates of Exercise SBP and HR  
Spartano et al

quartiles of exercise HR because the prognostic implications of a high exercise HR are less clear. A 2-sided P<0.05 was considered statistically significant. Collinearity diagnostic testing did not reveal highly intercorrelated predictor variables that could affect the models tested. All analyses were performed with the use of SAS version 9.3 (SAS Institute).

Results
We analyzed 1231 adults in the Framingham Offspring Study who attended 2 routine examinations almost 2 decades apart. The mean age at baseline was 39 years, with a mean age at follow-up of 58 years (Table 1). Over 2 decades, people gained weight: the mean BMI was 24.2 kg/m² at baseline and 27.1 kg/m² at follow-up. Hypertension prevalence rose from 4% to 14% of participants, and 3.4% developed new-onset DM. In contrast, many smokers quit: there were 32% smokers at baseline but only 14% at follow-up. Average SBP response to exercise (stage 2) was 151 mm Hg at baseline and 163 mm Hg at follow-up; average exercise HR (stage 2) was 131 bpm at baseline and 128 bpm at follow-up.

Correlates of Exercise SBP at Baseline and Follow-up
Baseline exercise SBP related positively to age, male sex, BMI, and resting SBP but negatively to resting HR (Table 2). Roughly, increments of 5 years in age and 1-mm Hg resting SBP or 1 kg/m² BMI were associated with a 1-mm Hg higher baseline exercise SBP, whereas a decrement of 8-bpm in resting HR had the same effect. At follow-up (examination 7), exercise SBP associated positively with age, BMI, resting SBP, resting HR, smoking, TC/HDL, and prevalent DM.

When we analyzed follow-up exercise SBP (stage 2) taking into account baseline exercise SBP, we found higher exercise SBP related to older age, female sex, higher baseline resting SBP and HR, and between-examination increases in resting SBP, resting HR, BMI, and new-onset DM (Table 3). In addition, smoking and high TC/HDL at baseline were associated with higher exercise SBP at follow-up. An increase between examinations of 1 kg/m² in BMI was associated with 1–mm Hg higher exercise SBP at follow-up; new-onset DM was associated with 6–mm Hg higher exercise SBP; and smokers at baseline had 5–mm Hg higher exercise SBP at follow-up. Age, sex, and baseline exercise SBP accounted for 28.8% of the variance in exercise SBP at follow-up (R²=0.288, data not shown), whereas the other correlates listed in Table 3 accounted for an additional 22.5% of the variance in exercise SBP at follow-up (R²=0.513 for full model, Table 3).

Correlates associated with being in the highest quartile of exercise SBP at follow-up (≥180 mm Hg) were displayed in Table 4. Similar to linear regression analysis described here, we found that older age, higher baseline resting SBP and HR, and between-examination increases in resting SBP, resting HR, and BMI were predictive of placement in the highest quartile of exercise SBP at follow-up, after adjusting for other

Table 1. Characteristics of the Framingham Offspring Cohort at Baseline and Follow-up (N=1231)

| Characteristics         | Baseline (Examination 2) | Follow-up (Examination 7) | P Value |
|-------------------------|--------------------------|---------------------------|---------|
| Age, y (min, max)       | 39±8 (17, 64)            | 58±8 (35, 81)             | <0.0001 |
| Women, n (%)            | 673 (55)                 | 673 (55)                  | —       |
| BMI, kg/m²              | 24.2±3.6                 | 27.1±4.5                  | <0.0001 |
| Current smoking, n (%)  | 394 (32)                 | 167 (14)                  | <0.0001 |
| Hypertension, n (%)     | 51 (4)                   | 167 (14)                  | <0.0001 |
| Diabetes mellitus, n (%)| —                        | 42 (3)                    | —       |
| TC/HDL                  | 4.1±1.4                  | 4.0±1.3                   | 0.03    |
| Resting SBP, mm Hg      | 114±12                   | 121±15                    | <0.0001 |
| Exercise SBP, mm Hg     | 151±21                   | 163±24                    | <0.0001 |
| Resting HR, bpm         | 64±10                    | 65±10                     | 0.03    |
| Exercise HR, bpm        | 131±19                   | 128±19                    | <0.0001 |

Values are mean±SD or n (%). Exercise SBP and HR were measured during stage 2 of the exercise treadmill test. BMI indicates body mass index; bpm, beats per minute; HDL, high-density lipoprotein cholesterol; HR, heart rate; SBP, systolic blood pressure; TC, total cholesterol.

Table 2. Multivariable Linear Regression Analysis* of Cross-sectional Correlates of Exercise SBP at Baseline and Follow-up

| Variable, Increment | Exercise SBP at Baseline (Examination 2), mm Hg | Exercise SBP at Follow-up (Examination 7), mm Hg |
|---------------------|-------------------------------------------------|-------------------------------------------------|
| Age, per 10 y       | 2.2 [1.1]                                      | 6.0 [0.7]                                       |
| Women (vs men)      | −7.1 [1.1]                                     | −0.5 [1.2]                                     |
| Resting SBP, per 10 mm Hg | 8.5 [0.5]                                      | 7.6 [0.4]                                      |
| Resting HR, per 10 bpm | −1.2 [0.5]                                     | 3.3 [0.5]                                      |
| TC/HDL, per unit    | 0.6 [0.4]                                      | 1.1 [0.4]                                      |
| Smoking (vs nonsmokers) | 0.8 [1.0]                                      | 4.7 [1.6]                                      |
| BMI, per 1 kg/m²     | 0.9 [0.1]                                      | 0.7 [0.1]                                      |
| DM (vs no DM)       | —                                               | 6.8 [2.9]                                      |

R² for full model, Table 3). *Regression model for correlates of exercise SBP at follow-up also adjusted for lipid medications at follow-up. There were few cases of DM or people taking lipid medications at baseline, so they were not included in the baseline model. Exercise SBP was measured during stage 2 of the exercise treadmill test.

DOI: 10.1161/JAHA.115.002821

Journal of the American Heart Association

3

Page of a document with text extracted, containing a table and a discussion about the effects of exercise on blood pressure and heart rate. The text explains the analysis of a study conducted over 2 decades, showing changes in BMI, blood pressure, and other factors. It also includes a table with characteristics of the Framingham Offspring Cohort and another table detailing the correlates of exercise SBP at baseline and follow-up.
Correlates of Exercise SBP and HR
Spartano et al

DOI: 10.1161/JAHA.115.002821

Correlates of Exercise SBP and HR at Baseline and Follow-up

In cross-sectional data (Table 5), higher resting HR, BMI, and female sex were associated with higher exercise HR (stage 2), whereas smokers had 2- to 3-bpm lower exercise HR. TC/HDL was only significantly associated with exercise HR at baseline. In our longitudinal data analysis, higher follow-up exercise HR (taking into account baseline exercise HR) was associated with older age, female sex, and baseline resting HR, plus interim increases in resting HR and BMI (Table 6). An increase between examinations of 3 kg/m² in BMI or 3-bpm resting HR was associated with 2-bpm higher exercise HR at follow-up. Age, sex, and baseline exercise HR accounted for 38.4% of the variance in exercise HR at follow-up ($R^2=0.384$, data not shown), whereas the other correlates listed in Table 6 accounted for an additional 13.2% of the variance in exercise HR at follow-up ($R^2=0.516$ for full model, Table 6).

Discussion

We assessed correlates of submaximal exercise variables at a baseline examination and again 2 decades later in a large cohort of adults who were relatively healthy—that is, not taking β-blocker or antihypertension medication. We found several CVD risk factors associated with exercise responses at baseline and at follow-up 2 decades later. Follow-up exercise responses also related to interim changes in some risk factors (notably BMI, as well as resting SBP and HR). Traditional CVD risk factors at baseline, age, male sex, and resting SBP were associated with higher exercise SBP; whereas blood lipid level was the only traditional CVD risk factors including baseline exercise SBP. Sex and development of DM, on the other hand, did not significantly relate to being in the highest exercise SBP quartile at follow-up (after adjusting for baseline exercise SBP and other factors), although they were significantly associated with exercise SBP at follow-up in linear regression analysis; however, quitting smoking was a significant predictor of remaining in the lowest 3 quartiles of exercise SBP at follow-up compared with continuing to smoking.

Correlates of Exercise HR at Baseline and Follow-up

Table 3. Multivariable Linear Regression Analysis* to Assess Correlates of Exercise SBP at Follow-up, Adjusting for Baseline Exercise SBP ($R^2=0.513$ for the Model)

| Variable at Baseline or Change From Baseline, Increment | Exercise SBP at Follow-up (Examination 7), mm Hg (Adjusting for Baseline Exercise SBP) |
|---------------------------------------------------------|-------------------------------------------------------------------------------------|
|                                                        | β-Est. [SE] | P Value |
| Age, per 10 y                                          | 5.0 [0.7]    | <0.0001 |
| Women (vs men)                                         | 3.8 [1.3]    | 0.003   |
| Baseline resting SBP, per 10 mm Hg                     | 5.9 [0.6]    | <0.0001 |
| Δ Resting SBP, per 10 mm Hg                            | 6.4 [0.4]    | <0.0001 |
| Baseline resting HR, per 10 bpm                         | 3.2 [0.6]    | <0.0001 |
| Δ Resting HR, per 10 bpm                                | 4.1 [0.6]    | <0.0001 |
| Baseline TC/HDL, per unit                               | 1.0 [0.5]    | 0.04    |
| Δ TC/HDL, per unit                                      | 0.7 [0.5]    | 0.17    |
| Baseline smoking (vs nonsmokers)                        | 4.8 [1.6]    | 0.003   |
| Smoking cessation (yes vs no)                           | –3.3 [1.8]   | 0.07    |
| Baseline BMI, per 1 kg/m²                               | 0.2 [0.2]    | 0.34    |
| Δ BMI, per 1 kg/m²                                      | 1.0 [0.2]    | <0.0001 |
| New-onset DM (yes vs no)                                | 5.9 [2.9]    | 0.04    |

Table 4. Multivariable Logistic Regression* to Assess Correlates Associated With the Highest Exercise SBP Quartile ($\geq$180 mm Hg) at Follow-up, Adjusting for Baseline Exercise SBP

| Variable at Baseline or Change From Baseline, Increment | Exercise SBP at Follow-up (Examination 7), mm Hg (Adjusting for Baseline Exercise SBP) |
|---------------------------------------------------------|-------------------------------------------------------------------------------------|
|                                                        | Odds Ratio [95% CI] | P Value |
| Age, per 10 y                                          | 1.58 [1.26–1.97]    | <0.0001 |
| Women (vs men)                                         | 0.80 [0.53–1.21]    | 0.29    |
| Baseline resting SBP, per 10 mm Hg                     | 1.85 [1.53–2.25]    | <0.0001 |
| Δ Resting SBP, per 10 mm Hg                            | 1.80 [1.58–2.05]    | <0.0001 |
| Baseline resting HR, per 10 bpm                         | 1.46 [1.19–1.79]    | 0.0003  |
| Δ Resting HR, per 10 bpm                                | 1.47 [1.22–1.77]    | <0.0001 |
| Baseline TC/HDL, per unit                               | 1.05 [0.91–1.22]    | 0.51    |
| Δ TC/HDL, per unit                                      | 0.99 [0.84–1.17]    | 0.90    |
| Baseline smoking (vs nonsmokers)                        | 2.36 [1.42–3.93]    | 0.0009  |
| Smoking cessation (yes vs no)                           | 0.47 [0.26–0.84]    | 0.01    |
| Baseline BMI, per 1 kg/m²                               | 1.00 [0.95–1.05]    | 0.97    |
| Δ BMI, per 1 kg/m²                                      | 1.13 [1.06–1.20]    | 0.0002  |
| New-onset DM (yes vs no)                                | 1.95 [0.90–4.25]    | 0.09    |

BMI indicates body mass index; bpm, beats per minute; DM, diabetes mellitus; HDL, high-density lipoprotein cholesterol; HR, heart rate; SBP, systolic blood pressure; TC, total cholesterol.

*Regression model also adjusted for baseline exercise SBP and change in lipid medications. Exercise SBP was measured during stage 2 of the exercise treadmill test; change variables (Δ) were calculated as the change from baseline to follow-up for the continuous variables and change in status for the categorical variables.

*Logistic regression model also adjusted for baseline exercise SBP and change in lipid medications. Exercise SBP was measured during stage 2 of the exercise treadmill test; change variables (Δ) were calculated as the change from baseline to follow-up for the continuous variables and change in status for the categorical variables.
factor associated with higher exercise HR at baseline (older age, male sex, and smoking status were associated with lower exercise HR at baseline). This investigation also suggests that development of DM in midlife is associated with a higher SBP response to exercise (adjusting for baseline exercise SBP) but was not predictive of being in the highest quartile of exercise SBP at follow-up. Smoking and higher blood lipid levels at the baseline examination were also associated with higher follow-up exercise SBP despite not being independently associated with baseline exercise SBP. Importantly, quitting smoking (compared with continuing to smoke) was associated with a lower risk of being in the highest quartile of exercise SBP at follow-up.

On average, American adults gain weight each year throughout midlife.16,17 Weight gain is also associated with a decrease in physical fitness18 and increased resting HR19 and may be associated with increased arterial stiffness in young adults20 (although supporting evidence is not as clear in middle-aged adults).21,22 Elevated resting HR is a measure of greater sympathetic activation and lower physical fitness, which may directly impact arterial stiffness21,23,24 and CVD risk.25 Exaggerated SBP exercise response has been linked to CVD risk, and it is also influenced by arterial stiffness and cardiorespiratory fitness.9 In the current investigation, greater between-examination weight gain was associated with higher follow-up exercise SBP and HR, adjusting for baseline exercise SBP and other covariates. A number of possible mechanisms may be responsible for these observations. Circulating metabolic factors including insulin, glucose, or inflammatory factors are elevated with weight gain, which may contribute to vascular dysfunction.26,27 We observed an association between the development of DM and increase in exercise SBP (after adjusting for changes in BMI), thus supporting the potential role of metabolic factors in increasing exercise SBP; but DM development did not predict placement in the highest quartile of exercise SBP, so it may not be the most important factor relating to exaggerated exercise SBP. Additionally, a higher body weight imposes a greater work load on the cardiovascular system during exercise, which may explain the impact of weight gain on exercise SBP and HR at follow-up.

The timing of risk factor exposure may also play a role in their pathogenic consequences. Smoking status and an unfavorable lipid profile did not significantly affect exercise SBP at baseline but were associated with higher exercise SBP at the follow-up examination. Our investigation demonstrates that being a smoker or having an unfavorable lipid profile in early adulthood has consequences that may not be apparent until years later, as supported by previous studies.12

### Table 5. Multivariable Linear Regression Analysis* of Cross-sectional Correlates of Exercise HR at Baseline and Follow-up

| Variable, Increment | Exercise HR at Baseline (Examination 2), bpm | Exercise HR at Follow-up (Examination 7), bpm |
|---------------------|---------------------------------------------|----------------------------------------------|
| Age, per 10 y       | −1.1 [0.5]                                  | 1.4 [0.5]                                    |
| Women (vs men)      | 19.2 [1.1]                                  | 14.1 [0.9]                                  |
| Resting SBP, per 10 mm Hg | 0.5 [0.4] | <0.0001                | 8.0 [0.4] | <0.0001 |
| Resting HR, per 10 bpm | 6.9 [0.4] | <0.0001                | 4.0 [0.4] | 0.31 |
| TC/HDL, per unit     | 1.1 [0.4]                                  | 0.003                                        | 0.4 [0.4] | 0.31 |
| Smoking (vs nonsmokers) | −2.0 [1.0]      | 0.04                             | −2.5 [1.3] | 0.05 |
| BMI, per 1 kg/m²     | 0.8 [0.1]                                  | <0.0001                                     | 0.5 [0.1] | <0.0001 |
| DM (vs no DM)        | —                                          | 0.2 [2.4]                                  | 0.92 |

BMI indicates body mass index; bpm, beats per minute; DM, diabetes mellitus; HDL, high-density lipoprotein cholesterol; HR, heart rate; SBP, systolic blood pressure; TC, total cholesterol.

*Regression model also adjusted for smoking status, metabolic factors including insulin, glucose, or inflammatory factors, and other covariates.

### Table 6. Multivariable Linear Regression Analysis* to Assess Correlates of Exercise HR at Follow-up, Adjusting for Baseline Exercise HR (R²=0.516 for the Model)

| Variable at Baseline or Change From Baseline, Increment | Exercise HR at Follow-up (Examination 7), bpm (Adjusting for Baseline Exercise HR) |
|--------------------------------------------------------|----------------------------------------------------------------------------------|
| Age, per 10 y                                          | 1.9 [0.5]                                                                        |
| Women (vs men)                                         | 6.2 [1.1]                                                                        |
| Baseline resting SBP, per 10 mm Hg                     | 0.3 [0.4]                                                                        |
| ∆ Resting SBP, per 10 mm Hg                           | −0.3 [0.3]                                                                        |
| Baseline resting HR, per 10 bpm                        | 5.1 [0.5]                                                                        |
| ∆ resting HR, per 10 bpm                               | 6.6 [0.4]                                                                        |
| Baseline TC/HDL, per unit                              | 0.4 [0.4]                                                                        |
| ∆ TC/HDL, per unit                                     | 0.08 [0.4]                                                                       |
| Baseline smoking (vs nonsmokers)                       | 0.6 [1.2]                                                                        |
| Smoking cessation (yes vs no)                          | 1.5 [1.4]                                                                        |
| Baseline BMI, per 1 kg/m²                              | −0.02 [0.1]                                                                      |
| ∆ BMI, per 1 kg/m²                                     | 0.6 [0.1]                                                                        |
| New-onset DM (yes vs no)                               | −0.6 [2.2]                                                                       |

BMI indicates body mass index; bpm, beats per minute; DM, diabetes mellitus; HDL, high-density lipoprotein cholesterol; HR, heart rate; SBP, systolic blood pressure; TC, total cholesterol.

*Regression model also adjusted for baseline exercise HR and change in lipid medications. Exercise HR was measured during stage 2 of the exercise treadmill test; change variables (Δ) were calculated as the change from baseline to follow-up for the continuous variables and change in status for the categorical variables.
Smoking damages the artery wall and contributes to arterial stiffness, but the effect of smoking on resting BP has not been consistent across large observational studies even after adjusting for age and weight status. Smoking has also been implicated in diminishing the baroreflex sensitivity, which disrupts the control of BP and HR, increasing the variability of ambulatory BP and HR. The effects of smoking on impaired baroreflex sensitivity may also explain our observation that baseline smoking was associated with an elevated exercise SBP at follow-up. Smoking has been reported to increase resting HR but has also been observed to reduce exercise HR in previous studies. In agreement, our results support a relationship between smoking status and lower exercise HR across midlife.

Reversibility of vascular damage and dysfunction by smoking cessation is less well investigated. Small studies have not found cessation of smoking to affect large artery compliance, and it is associated with other cardiovascular benefits. We observed that those who quit smoking had a 53% lower risk of having exaggerated exercise SBP at follow-up compared with those who continued smoking. However, we did not consider the duration of smoking or smoking cessation or quantify the pack-years of smoking, which may limit our findings. Results from this investigation suggest that it may be more important to avoid the development of risk factors in the first place, such as smoking and unfavorable lipid profile, which were associated with higher exercise SBP at follow-up, regardless of changes in these risk factors.

Strengths and Limitations
We may have introduced a selection bias due to exclusions; however, the design may also be a strength, because it allowed us to examine relations of exercise responses at 2 time points with CVD risk factors in healthy adults. The study sample was also predominantly composed of white individuals of European descent. Therefore, results may have limited generalizability to other ethnicities. We chose to focus this study on the correlates of submaximal exercise SBP, the submaximal exercise response most strongly associated with vascular dysfunction, instead of submaximal exercise DBP, which may be affected by declining left ventricular function and often decreases with age (data not shown). We also chose not to focus on normal versus abnormal HR responses in the present analysis but decided instead to analyze how risk factors relate to exercise HR responses and to the change in these responses over time (in a linear regression analyses). The relations of traditional risk factors to exercise DBP and abnormal HR responses will be important to assess in future studies.

In the current investigation, we used an abbreviated exercise test, equivalent to 6 minutes of increasing exercise until a maximum of 2.5 mph (or a pace of 24 minutes per mile) at a moderate 12% grade. Use of a standardized, submaximal test further improves the strength of our study design. Athletes may have a slower rate of increased BP and HR during moderate exercise but often reach very high levels of SBP during maximal exercise; thus, the “dose of exercise” must be accounted for, as an exaggerated SBP response to maximal exercise can paradoxically be a marker of high fitness level. This phenomenon may explain the findings in some studies that reported a lack of association of SBP at maximal exercise with CVD risk. At lower levels of exercise, such as the design used in the current investigation, we were able to observe the rate at which SBP and HR rose during exercise, which has been suggested as a better marker for target organ damage than maximal exercise hemodynamics, because the dose of exercise was the same for all participants. However, we are unable to control for the percent oxygen consumption that participants achieve or whether they exhibit chronotropic incompetence during the submaximal ETT. Additionally, the fitness level of participants would affect their responses to low levels of exercise, as in our investigation. Indeed, SBP and HR responses to a maximal exercise test could provide incremental information above and beyond that provided by the present investigation, but these data were unavailable in the current study (an unavoidable limitation because of the submaximal exercise protocols used at the FHS examinations). It is noteworthy, though, that moderate levels of exercise (eg, the submaximal ETT that was used in our investigation) may mimic the type of moderate walking speed encountered during normal daily activities.

Conclusion
Our investigation suggests that presence of CVD risk factors and their worsening over time are associated with a higher exercise SBP response both at baseline and at a follow-up examination 2 decades later. Our findings also underscore the importance of maintaining or adopting a healthy risk factor profile over the life course to promote better exercise responses in later life.

Sources of Funding
This study was funded by the Framingham Heart Study’s National Heart, Lung, and Blood Institute contract (N01-HC25195, HHSN268201500001I) with additional support from the following National Institutes of Health grants: (R01-AG047645, R01-HL131029, T32-HL072224) and American Heart Association award (15GPSGC24800006).
Disclosures
The authors have no conflicts of interest to report.

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DOI: 10.1161/JAHA.115.002821