

## Prevalence, Correlates, and Prognosis of Healthy Vascular Aging in a Western Community-Dwelling Cohort The Framingham Heart Study

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See Editorial Commentary, pp 229–231

**Abstract**—Hypertension and increased vascular stiffness are viewed as inevitable parts of aging. To elucidate whether the age-related decrease in vascular function is avoidable, we assessed the prevalence, correlates, and prognosis of healthy vascular aging (HVA) in 3196 Framingham Study participants aged  $\geq 50$  years. We defined HVA as absence of hypertension and pulse wave velocity  $< 7.6$  m/s (mean+2 SD of a reference sample aged  $< 30$  years). Overall, 566 (17.7%) individuals had HVA, with prevalence decreasing from 30.3% in people aged 50 to 59 to 1% in those aged  $\geq 70$  years. In regression models adjusted for physical activity, caloric intake, and traditional cardiovascular disease (CVD) risk factors, we observed that lower age, female sex, lower body mass index, use of lipid-lowering drugs, and absence of diabetes mellitus were cross-sectionally associated with HVA ( $P < 0.001$  for all). A unit increase in a cardiovascular health score (Life's Simple 7) was associated with 1.55-fold (95% confidence interval, 1.38–1.74) age- and sex-adjusted odds of HVA. During a follow-up of 9.6 years, 391 CVD events occurred. In Cox regression models adjusted for traditional CVD risk factors, including blood pressure, HVA was associated with a hazard ratio of 0.45 (95% confidence interval, 0.26–0.77) for CVD relative to absence of HVA. Although HVA is achievable in individuals acculturated to a Western lifestyle, maintaining normal vascular function beyond 70 years of age is challenging. Although our data are observational, our findings support prevention strategies targeting modifiable factors and behaviors and obesity, in particular, to prevent or delay vascular aging and the associated risk of CVD. (*Hypertension*. 2017;70:267-274. DOI: 10.1161/HYPERTENSIONAHA.117.09026.) • [Online Data Supplement](#)

**Key Words:** aging ■ blood pressure ■ epidemiology ■ hypertension ■ vascular stiffness

Until some decades ago, the rule-of-thumb definition of normal systolic blood pressure was 100 plus your age. However, this cutoff has not been acceptable after antihypertensive treatment was unequivocally shown to reduce cardiovascular disease (CVD) risk in also elderly hypertensive patients.<sup>1–3</sup> Although hypertension at old age is no longer considered harmless, it is still highly prevalent. In middle-aged and elderly nonhypertensive individuals, the residual lifetime risk for hypertension was estimated to be 90%.<sup>4</sup> Age-related increases in arterial stiffness and blood pressure are thereby widely accepted as an inevitable part of the aging process in acculturated societies, further exemplified by the widespread use of the term essential hypertension. However, age-associated increase in blood pressure is not common in some populations leading traditional

hunter-gatherer lifestyles (although these data are limited by modest sample sizes).<sup>5–10</sup>

An individual's vascular age can be crudely approximated from systolic blood pressure and pulse pressure, but arterial wall imaging or measurement of arterial stiffness can be used to obtain additional complementary information. Aortic pulse wave velocity (PWV), for example, is a commonly used surrogate marker of arterial stiffness that is strongly related to CVD morbidity and may be considered a physiological method for quantifying arterial aging.<sup>11–14</sup>

The prevalence, correlates, and prognosis of healthy vascular aging (HVA; ie, lack of age-related increases in arterial stiffness and blood pressure) in a contemporary Western cohort are incompletely understood. The aims of our study were 3-fold: (1) to operationalize the concept of HVA using

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2 easily measured vascular traits, (2) to assess the prevalence and correlates of HVA in a cohort acculturated to a Western lifestyle, and (3) to evaluate the magnitude of CVD risk associated with unhealthy versus HVA.

## Methods

### Participants

Because age-related arterial stiffening is absent in certain populations, we submit that the definition of normal vascular function should be the same in all age groups.<sup>5-9</sup> To capture a distinct sample of individuals who have experienced HVA, we considered only participants in late middle age or older (aged  $\geq 50$  years) who attended examination 7 (1998–2001) or 8 (2005–2008) of the Offspring cohort (n=3371) and examination 1 of the Third-Generation (n=606; 2002–2005) cohort of the Framingham Heart Study (Figure S1 in the [online-only Data Supplement](#)). Offspring cohort participants were primarily drawn from examination cycle 7, or alternatively from examination 8 if data from examination 7 were missing. We excluded participants with prevalent CVD (see Cardiovascular Outcomes section for detailed description), missing tonometry data, or missing covariates (Figure S1 in the [online-only Data Supplement](#)). To examine the association between American Heart Association's Life's Simple 7 score and HVA, we identified a subset of 2086 Offspring cohort participants (of 3197 included in the main analyses) who had data available for all components of the score. Boston University Medical Center's Institutional Review Board approved all study protocols, and participants provided written informed consent. The characteristics and study protocols of the 2 cohorts have been previously published in detail.<sup>15,16</sup>

### Baseline Evaluation

At baseline, all participants provided a medical history and underwent a cardiovascular targeted physical examination and laboratory assessment of CVD risk factors.<sup>15</sup> We assessed the participants for cigarette smoking and diabetes mellitus (fasting glucose level of  $\geq 7$  mmol/L or the use of hypoglycemic medications). In addition, we measured blood pressure (mean of 2 auscultatory values obtained by a physician using a mercury column sphygmomanometer on the left arm of seated participants), PWV, body mass index (BMI), serum total cholesterol, and high-density lipoprotein cholesterol concentrations. We defined blood pressure as the mean of 2 readings. Participants underwent assessments of physical activity, using a questionnaire and calculation of the Framingham physical activity index, and assessments of diet, using data collected via the Harvard semiquantitative food frequency questionnaire.<sup>17,18</sup>

### Measurements for Arterial Stiffness and Definition of HVA

We evaluated arterial stiffness with carotid–femoral PWV.<sup>19</sup> PWV is directly related to aortic wall stiffness. We performed arterial tonometry as previously described after  $\geq 5$  minutes of rest in the supine position.<sup>20,21</sup> All measurements were performed on the right side of the body. Arterial tonometry with concurrent ECG was obtained for the femoral and carotid arteries. We estimated the pulse wave transit distances by measuring the direct surface distance between the suprasternal notch and the carotid or femoral sites. We accounted for parallel transmission along the brachiocephalic and carotid arteries and around the aortic arch by taking the difference in distances from suprasternal notch to femoral and carotid sites. The methodology for PWV measurement remained the same during all study cycles. PWV was defined as the corrected distance divided by the carotid–femoral transit time delay. We inverted PWV to reduce heteroscedasticity and multiplied it by  $-1$  to restore direction of effect.

We defined HVA for individuals  $\geq 50$  years as having both of the following:

1. normotensive blood pressure, which constituted  $<140$  mm Hg for systolic and  $<90$  mm Hg for diastolic blood pressure and absence of hypertensive treatment.
2. PWV of  $<7.6$  m/s, which was equivalent to the mean+2 SD value obtained from a reference sample of individuals who were aged  $<30$  years, with optimal or normal blood pressures and no additional CVD risk factors.<sup>22</sup>

### Cardiovascular Health Score

For each participant, we calculated a cardiovascular health score by recoding 7 modifiable risk factors as dichotomous variables according to the American Heart Association's Life's Simple 7 score—a metric that is used to measure and promote healthy lifestyle behaviours.<sup>23</sup> The 7 components of the cardiovascular health score are fasting blood glucose, cholesterol, resting blood pressure, BMI, self-reported smoking status, dietary quality, and physical activity (Table S1). We modified the score by excluding blood pressure because it is a part of the outcome variable in this study. Each component of the cardiovascular health was allocated a score of 1 indicating the American Heart Association's ideal category for that metric (versus 0 for nonideal metric); thus, the cardiovascular health score could vary from a minimum of 0 (indicating poor cardiovascular health) to a maximum of 6 (reflecting ideal cardiovascular health).

### Cardiovascular Outcomes

We used 2 composite CVD end points in our study: hard CVD events and CVD events. Hard CVD was a composite end point of cardiovascular death, fatal or nonfatal myocardial infarction, and stroke. CVD was a composite end point of angina pectoris, unstable angina (prolonged ischemic episode with documented reversible ST-segment changes), transient ischemic attack, heart failure, intermittent claudication, and all end points included in hard CVD. We obtained medical records for all hospitalizations and physician visits related to CVD during follow-up, which were reviewed by an adjudication panel consisting of 3 investigators. Criteria for these CVD events have been described previously.<sup>24</sup>

### Statistical Methods

We assessed baseline characteristics according to HVA status, overall, and by sex. We compared prevalence of HVA among age groups using the  $\chi^2$  test.

We examined cross-sectional correlates of HVA using multivariable stepwise logistic regression with backward selection, retaining covariates with  $P < 0.10$ . In addition to cohort (Offspring versus Third Generation), we derived the other covariates for the logistic regression models from the Framingham 10-year CVD risk score (ie, age, sex, cohort, BMI, smoking status, diabetes mellitus, serum total cholesterol, and high-density lipoprotein cholesterol). We included total caloric intake and the Framingham Physical Activity Index in a separate model (2671 participants had those data). We standardized continuous variables and tested for statistical interactions with age (using median age) and sex interactions by entering corresponding cross-product terms into the models. We also performed a sensitivity analysis in 3111 individuals with data available using a 3-category variable to define hyperglycemia: normal glycemia (plasma fasting glucose  $<5.6$  mmol/L), impaired fasting glucose (plasma fasting glucose 5.6–6.9 mmol/L), and diabetes mellitus (plasma fasting glucose  $\geq 7$  mmol/L or use of hypoglycemic medications). To characterize individuals with HVA in more detail beyond traditional risk factors, we determined serum high-sensitivity C-reactive protein, interleukin-6, estimated glomerular filtration rate, homeostatic model assessment insulin resistance index, urine albumin:creatinine ratio levels, and a genetic risk score for coronary artery disease in 1418 to 3190 individuals with such data available. We used generalized linear models to compare age- and sex-adjusted means of genetic, inflammatory, renal, and metabolic biomarker levels between individuals with and without HVA. The methods for determining these biomarkers are described in more detail in the Methods section in the [online-only Data Supplement](#). Next, we calculated age- and sex-adjusted odds ratios (ORs) for HVA comparing participants who had health scores of 2 through 6 to those with scores of 0 to 1.

We examined associations between HVA and CVD outcomes using proportional hazards regression (Cox) models: plotting age-, sex-, and cohort-adjusted cumulative incidence functions<sup>25</sup> and also fitting multivariable-adjusted models. We performed a sensitivity analysis for risk of CVD outcomes using 3 alternative definitions for HVA: (1) blood pressure <140/90 mm Hg and PWV <8.1 m/s (corresponding to the 95th percentile for PWV in a healthy Framingham Heart Study reference sample <50 years of age),<sup>26</sup> (2) blood pressure <120/80 mm Hg and PWV <7.6 m/s, and (3) blood pressure <140/90 mm Hg and absence of coronary artery calcification (Agatston score 0). The latter analysis was performed in a subgroup of 1332 participants who underwent coronary artery calcium scoring, as previously described.<sup>27</sup> All analyses were performed with SAS software, version 9.4 (Cary, NC). We considered a 2-sided  $P < 0.05$  to be statistically significant.

## Results

Characteristics of the sample ( $n=3196$ ; mean age,  $62 \pm 9$  years; 56% women) according to HVA status are presented in Table 1. The characteristics of the included and excluded participants are shown in Table S2. Of the 490 people who were excluded because of prevalent CVD, only 14 (2.9%) were nonhypertensive and had a PWV <7.6 m/s. Among participants, 566 (17.7%) had HVA. Men and women with HVA had more favorable CVD risk profiles than others (Table 1). Prevalence of HVA decreased from 30.3% in people aged 50 to 59 to 1% in those aged  $\geq 70$  years (Figure 1;  $P < 0.001$ ).

In backward selection logistic regression modeling (Table 2), we observed that younger age, female sex, lower

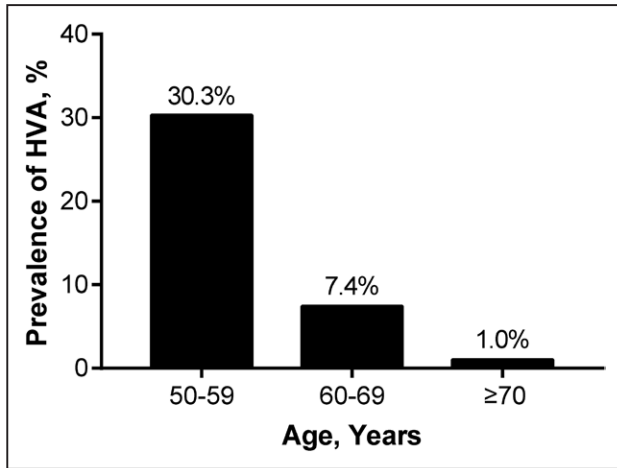
BMI, use of lipid-lowering drugs, and absence of diabetes mellitus ( $P < 0.001$  for all) were cross-sectionally associated with HVA. Current smoking, serum total cholesterol, and serum high-density lipoprotein cholesterol were not retained. No statistically significant interactions were observed between age or sex and any of the significant correlates of HVA in the multivariable model ( $P \geq 0.27$  for all). In a subsample of 2671 participants with data available, we also included physical activity index and total caloric intake in the model for HVA. Neither variable reached statistical significance ( $P \geq 0.10$  for both). In a sensitivity analysis using a 3-category variable for hyperglycemia, impaired fasting glucose (OR, 0.63; 95% confidence interval [CI], 0.50–0.81;  $P=0.03$ ) and diabetes mellitus (OR, 0.10; 95% CI, 0.03–0.32;  $P < 0.001$ ) were associated with lower odds of HVA compared with normal glycemia. The age- and sex-adjusted mean genetic, inflammatory, renal, and metabolic biomarker levels according to HVA status are presented in Table S3. We observed that individuals with HVA had lower interleukin-6, high-sensitivity C-reactive protein, and homeostatic model assessment insulin resistance index levels than participants with no HVA. No between-group differences were observed in renal function or in the genetic risk score for coronary artery disease.

The ORs for HVA according to the cardiovascular health score in 2086 participants (mean age,  $63.2 \pm 8.3$ ; 57.1% women) of the Offspring cohort are shown in Table 3. Compared with participants who achieved 0 to 1 goals, the

**Table 1. Baseline Characteristics According to HVA Status**

Characteristics	Overall		Men		Women	
	HVA (n=566)	No HVA (n=2630)	HVA (n=164)	No HVA (n=1240)	HVA (n=402)	No HVA (n=1390)
Cohort						
Offspring	402 (71)	2259 (86)	109 (66)	1042 (84)	293 (73)	1217 (88)
Third generation	164 (29)	371 (14)	55 (34)	198 (16)	109 (27)	173 (12)
Age, y	$55 \pm 4.7$	$63 \pm 8.6$	$54.8 \pm 4.9$	$62.4 \pm 8.6$	$55.1 \pm 4.7$	$63.6 \pm 8.6$
Women	402 (71)	1390 (53)	0 (0)	0 (0)	402 (100)	1390 (100)
Systolic BP, mm Hg	$113 \pm 11$	$130 \pm 18$	$116 \pm 10$	$130 \pm 16$	$111 \pm 11$	$130 \pm 19$
Diastolic BP, mm Hg	$71 \pm 8$	$76 \pm 10$	$74 \pm 7$	$77 \pm 10$	$70 \pm 8$	$74 \pm 10$
PWV, m/s	$6.8 \pm 0.5$	$10.4 \pm 3.2$	$6.9 \pm 0.5$	$10.6 \pm 3.3$	$6.8 \pm 0.5$	$10.3 \pm 3.2$
HTN medication	0 (0)	1103 (42)	0 (0)	531 (43)	0 (0)	572 (41)
BMI, kg/m <sup>2</sup>	$25.1 \pm 4$	$28.3 \pm 5.1$	$26.2 \pm 3.2$	$28.8 \pm 4.4$	$24.7 \pm 4.2$	$27.9 \pm 5.6$
Diabetes mellitus	3 (0.5)	286 (10.9)	1 (0.6)	156 (12.6)	2 (0.5)	130 (9.4)
Current smoker	83 (15)	275 (10)	18 (11)	135 (11)	65 (16)	140 (10)
Cholesterol, mmol/L	$5.2 \pm 0.9$	$5.1 \pm 1$	$5.1 \pm 0.9$	$4.9 \pm 0.9$	$5.2 \pm 0.9$	$5.4 \pm 1$
HDL cholesterol, mmol/L	$1.7 \pm 0.5$	$1.4 \pm 0.5$	$1.3 \pm 0.3$	$1.2 \pm 0.4$	$1.8 \pm 0.5$	$1.6 \pm 0.5$
Lipid-lowering medication	64 (11)	712 (27)	26 (16)	353 (29)	38 (9)	359 (26)
Physical activity index	$37.6 \pm 6.4$	$37.9 \pm 6.6$	$38.5 \pm 7.3$	$38.5 \pm 7.3$	$37.3 \pm 5.9$	$37.3 \pm 5.8$
Total caloric intake, kcal/d	$1855 \pm 591$	$1868 \pm 662$	$2078 \pm 642$	$2000 \pm 727$	$1769 \pm 548$	$1751 \pm 574$

Data are shown as mean  $\pm$  SD for continuous variables and as n (%) for categorical variables. Data on physical activity index and total caloric intake were available for 2887 and 2833 participants, respectively. BMI indicates body mass index; BP, blood pressure; HDL, high-density lipoprotein; HTN, hypertension; HVA, healthy vascular aging; and PWV, pulse wave velocity.



**Figure 1.** Prevalence of healthy vascular aging in age groups of 50 to 59 (n=1610), 60 to 69 (n=969), and ≥70 y (n=617). HVA indicates healthy vascular aging.

OR for HVA was significantly increased in participants who achieved 3 goals (OR, 3.11; 95% CI, 1.67–5.79). Participants who achieved 6 goals had 10.23-fold (95% CI, 3.85–27.16) odds of HVA. A 1-unit increase in the cardiovascular health score corresponded to 1.55-fold (95% CI, 1.38–1.74) odds of HVA.

During follow-up (median, 9.6 years), 391 developed CVD, which included 207 hard CVD events. The direct-adjusted plots for incidence of CVD and hard CVD are shown in Figure 2. Individuals with HVA had considerably lower age- and sex-adjusted risk of CVD (hazard ratio, 0.34; 95% CI, 0.20–0.57) and hard CVD (hazard ratio, 0.31; 95% CI, 0.15–0.64) in relation to individuals without HVA (Table 4). After adjusting for other traditional CVD risk factors, including systolic blood pressure, HVA was associated with a 0.45-fold (95% CI, 0.26–0.77) risk of CVD events and a 0.46-fold risk (95% CI, 0.22–0.96) of hard CVD events. No statistically significant interactions were observed between age or sex and HVA in the multivariable model ( $P \geq 0.34$  for all). We also performed 3 separate sensitivity analyses, in which HVA was defined as (1) blood pressure <140/90

**Table 2. Multivariable Logistic Regression for Odds of HVA vs No HVA**

Characteristics	OR for HVA (95% CI)	P Value
Age, y	0.20 (0.17–0.24)	<0.001
Female sex	2.10 (1.68–2.64)	<0.001
BMI, kg/m <sup>2</sup>	0.50 (0.44–0.57)	<0.001
Diabetes mellitus	0.12 (0.04–0.39)	<0.001
Lipid-lowering therapy	0.68 (0.50–0.93)	0.01
Total cholesterol, mmol/L	0.90 (0.80–1.005)	0.06

Five hundred sixty-six individuals had HVA, whereas 2630 did not. ORs for BMI, total cholesterol, and age are reported per 1-SD increase for comparability. ORs are adjusted for cohort type. High-density lipoprotein cholesterol and smoking did not meet the threshold *P* value of 0.10 and were not retained in the backward selection process. BMI indicates body mass index; CI, confidence interval; HVA, healthy vascular aging; and OR, odds ratio.

mmHg and PWV <8.1 m/s, (2) blood pressure <120/80 mmHg and PWV <7.6 m/s, or (3) blood pressure <140/90 mmHg and coronary artery calcium score of 0 (Table S4). In these sensitivity analyses, the multivariable-adjusted associations between HVA and CVD outcomes were statistically nonsignificant, except for the relationship between HVA defined as blood pressure <120/80 mmHg and PWV <7.6 m/s and CVD.

## Discussion

In the present investigation, we operationalize the theoretical construct of HVA using blood pressure and PWV. Although modest improvements in risk discrimination may be achieved using multivariable risk scores to define HVA (incorporating additional measures of vascular aging), we opted to use these 2 easily obtained metrics of vascular health for simplicity of interpretation of results. We observed that every sixth person aged ≥50 years had experienced HVA, defined as absence of hypertension and carotid–femoral PWV <7.6 m/s. However, HVA was virtually nonexistent in people aged ≥70 years. Modifiable risk factors included in American Heart Association's Life's Simple 7 score, and particularly low BMI, having no diabetes mellitus and hypercholesterolemia (lipid-lowering therapy and borderline significance for serum total cholesterol), were associated with HVA. Individuals with HVA had a markedly lower risk of CVD events, even after accounting for traditional CVD risk factors.

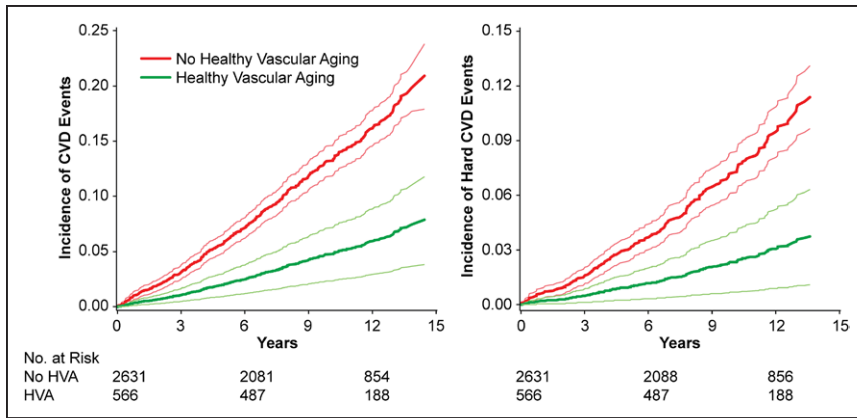
The concept of HVA may not have received notable attention previously because of the strong correlation between age and arterial stiffness.<sup>19,28</sup> A large part of recent research on vascular aging has, therefore, focused on early vascular aging, an even more rapid course of vascular aging that results in premature CVD manifestations.<sup>28</sup> However, both past and more contemporary research suggest that vascular aging, just as isolated systolic hypertension, should no longer be considered a part of normal aging. Studies performed on hunter-gatherers have demonstrated the low rates

**Table 3. Association of Cardiovascular Health Score With HVA (n=2086)**

Cardiovascular Health Score*	No. of Participants	No. With HVA	OR (95% CI)	P Value
Per 1-U increase	2086	312	1.55 (1.38–1.74)	<0.001
Goals achieved				
0–1	221	14	1 (reference)	...
2	562	51	1.62 (0.85–3.09)	0.15
3	625	95	3.11 (1.67–5.79)	<0.001
4	435	70	2.89 (1.52–5.50)	0.001
5	209	68	7.36 (3.75–14.44)	<0.001
6	34	14	10.23 (3.85–27.16)	<0.001

CI indicates confidence interval; HVA, healthy vascular aging; and OR, odds ratio.

\*One additional point for each low-risk health metric achieved (physical activity, diet, body mass index, smoking, total cholesterol, and fasting glucose). All analyses are adjusted for sex, age, and cohort type.



**Figure 2.** Direct-adjusted incidence curves for cardiovascular events. Curves are adjusted for age, sex, and cohort. Thin, light lines represent 95% confidence limits. CVD indicates cardiovascular disease; and HVA, healthy vascular aging.

of age-related increases in blood pressure,<sup>5-10</sup> PWV,<sup>7</sup> and CVD<sup>6</sup> in these populations. Although some of these studies included few individuals aged >50 years,<sup>10</sup> their results also showed that blood pressure levels and arterial stiffness in these populations increased with the level of Western acculturation and urbanization.<sup>6,7,9</sup> These interesting findings seem to be mainly driven by environmental, instead of genetic, factors because blood pressure levels and arterial stiffness in these populations were shown to increase with the level of Western acculturation and urbanization.<sup>6,7,9</sup> Our findings on the statistically nonsignificant differences in the genetic coronary artery disease risk scores also are consistent with this premise. More contemporary results from the Systolic Blood Pressure Intervention Trial (SPRINT) also imply that an individual's blood pressure should remain optimal even after middle age. In the SPRINT trial with a study population of hypertensive patients without diabetes mellitus aged ≥50 years, targeting a systolic blood pressure <120 mm Hg, as compared with <140 mm Hg, resulted in lower rates of major cardiovascular events and death from any cause. The SPRINT results were also similar in subgroups by age (<75 and ≥75 years), suggesting that lower is better applies to blood pressure values in all age groups and to treated and untreated individuals without diabetes mellitus. HVA should, therefore, be considered a universal goal. Our results demonstrate that HVA, defined as nonhypertension and PWV <7.6 m/s at ≥50 years of age, is achievable and provides an effective method to distinguish between individuals with low versus high cardiovascular risk. However, maintaining a youthful vascular function

beyond age 70 is extremely challenging, which underscores the need for lifelong prevention of arterial stiffening.

Our results demonstrate that maintaining a lifestyle and a cardiovascular risk profile that are in accord with the Life's Simple 7 health factors are important for preventing arterial aging.<sup>23</sup> Besides nonmodifiable risk factors, obesity and diabetes mellitus were the strongest correlates of HVA in our study. We also observed lower levels of inflammatory biomarkers and homeostatic model assessment insulin resistance index in individuals with HVA. Our findings, therefore, are consistent with the notion that insulin resistance and chronic low-grade inflammation, both closely related to obesity and diabetes mellitus, could be potential contributors to vascular aging.<sup>29</sup> Somewhat surprisingly, we did not observe an independent association between some cardiovascular risk factors, such as smoking, diet, and exercise, and HVA. In addition to lack of statistical power and small effect sizes, these findings may be also explained by the mediating effects of BMI on the relations of diet or exercise and HVA. Furthermore, the association between smoking and vascular function is not straightforward as paradoxically lower rates of hypertension and decreased arterial stiffness have been observed among smokers in some epidemiologic studies.<sup>30,31</sup> Although smoking, diet, and exercise may not be equally strong correlates of HVA as obesity, diabetes mellitus, or hypercholesterolemia, our results showed a gradual stepwise increase in the odds of HVA across the whole range of Life's Simple 7 score. Our results are, therefore, suggestive that controlling all the modifiable factors included in Life's Simple 7 is important for achieving HVA.

**Table 4. Risk of Cardiovascular Events Related to Healthy vs Unhealthy Vascular Aging (n=3196)**

Model	CVD (391 Events)		Hard CVD (207 Events)	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Model 1: adjusted for sex, age, and cohort	0.34 (0.20–0.57)	<0.001	0.31 (0.15–0.64)	0.002
Model 2: model 1+BMI, HDL-C, cholesterol, DM, lipid meds, and smoking	0.40 (0.23–0.68)	0.001	0.37 (0.18–0.77)	0.008
Model 3: model 2+systolic blood pressure	0.45 (0.26–0.77)	0.004	0.46 (0.22–0.96)	0.04

Only 15 CVD and 8 hard CVD events occurred in participants with healthy vascular aging. BMI indicates body mass index; CI, confidence interval; CVD, cardiovascular disease; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; and HR, hazard ratio.

Specifically, our results should not be interpreted to indicate that smoking, diet, or physical activity are not related to vascular aging. We have previously reported that physical activity (measured by accelerometry) is associated with lower vascular stiffness.<sup>32</sup>

In a previous study, the Multi-Ethnic Study of Atherosclerosis researchers examined a group of 165 individuals who had survived to  $\geq 70$  years of age, free of clinical CVD and also had limited subclinical vascular disease by a combination index of 3 separate parameters (coronary artery calcium  $< 25$ th percentile, carotid intima-media thickness  $< 25$ th percentile, and ankle-brachial index  $> 0.9$ ).<sup>33</sup> In accordance with our results, the authors found that younger age, female sex, and lower BMI were most strongly ( $P < 0.001$ ) associated with the combination index. In addition to these 3 factors, diabetes mellitus also seems to markedly decrease the odds of HVA—individuals with diabetes mellitus had  $> 8$ -fold lower odds of HVA than nondiabetics in our study. Considering that  $> 80\%$  of people with type 2 diabetes mellitus are also obese, our results highlight the importance of maintaining normal body weight in preventing cardiovascular aging.<sup>34</sup> Despite the marked reductions in the prevalence of cardiovascular risk factors, such as smoking and hypercholesterolemia in developed countries, there has been little success in preventing obesity—the most important risk factor for diabetes mellitus.<sup>35,36</sup> During the past 30 years, age-standardized mean global BMI has increased from 22 to 24 kg/m<sup>2</sup>, which conjointly with population growth and aging, has led to a near quadrupling of the number of adults with diabetes mellitus worldwide.<sup>37,38</sup> The impact of the global obesity epidemic is also reflected by recent plateauing of hypertension prevalence rates in the United States.<sup>39</sup> Healthy vascular aging will, therefore, likely remain infrequent unless adverse trends in population nutrition and BMI occur.<sup>40</sup>

We observed a 3-fold lower age- and sex-adjusted risk and a  $> 2$ -fold lower multivariable-adjusted risk of CVD in people with HVA relative to absence of HVA. Because the final model (Model 3 in Table 4) also included systolic blood pressure as a covariate, these results mainly reflect the poor CVD prognosis associated with arterial stiffening.<sup>12,19</sup> Although these estimates are not robust enough for HVA to be used as a screening method, they still emphasize the importance of vascular stiffening and arterial aging in the pathogenesis of CVD. In sensitivity analyses, we examined the association between HVA and CVD outcomes using 3 alternate definitions of HVA. Using a definition of blood pressure 140/90 mm Hg and a higher PWV threshold of  $< 8.1$  m/s, the risk estimates of CVD related to HVA were statistically nonsignificant, possibly reflecting lesser statistical power because of few events in the group with HVA; of note, point estimates for HVA in these analyses were all  $< 1$  and the  $P$  values were borderline statistical significant ( $< 0.10$ ). With the other 2 alternate definitions of HVA (a blood pressure threshold of 120/80 mm Hg instead of 140/90 mm Hg or coronary calcium scoring instead of PWV), the risk estimates were, although mainly nonsignificant, comparable to those observed in the primary analyses. However, because of the low number of CVD events among individuals with HVA, we lack statistical power to make any definite conclusions regarding these sensitivity analyses. In spite the fact that arterial stiffening, and

the increased CVD risk associated with it, can be detected with relative ease, treating it remains a considerable challenge for physicians. Lifestyle factors and certain antihypertensive drugs have been shown to reduce arterial stiffness mainly through lowering blood pressure, but there are currently no drugs that specifically target arterial stiffening.<sup>41,42</sup> The most promising drug candidates in this area are NO donors, drugs interfering with the arterial extracellular matrix, selective angiotensin type 2 receptor agonists, and agents reducing arterial calcification, but clinical data are still pending.<sup>41–43</sup> However, given the notable CVD risk associated with arterial stiffening, the clinical need for destiffening therapies remains significant.

Our study has certain limitations. First, our study sample consisted of predominantly white individuals, and our results may not be generalizable to the other races/ethnicities. This is a major limitation of our investigation given the known racial disparities in hypertension and hypertension-related outcomes.<sup>44</sup> Second, data on nutrition and physical exercise were not available for all individuals. Third, validated self-report questionnaires may not be the most accurate methods for assessing food intake and physical activity, despite being the most commonly used methods in epidemiologic settings. Fourth, we excluded from the present analyses individuals who died before reaching 50 years of age and had prevalent CVD. Nearly all individuals who were excluded because of prevalent CVD had unhealthy vascular aging. We, therefore, studied HVA in the context of fairly healthy aging (ie, absence of clinical disease). Fifth, some of the analyses in our study are cross-sectional (precluding any causal inferences) and raising the additional possibility of reverse causation between HVA and some of the exposure variables (such as lower ability to exercise in individuals with arterial stiffening).

## Perspectives

One in 6 individuals experienced HVA in our sample  $\geq 50$  years of age. Although HVA is achievable in individuals acculturated to a Western lifestyle, our results demonstrate that maintaining normal vascular function beyond age 70 is extremely challenging. Our data, which are observational, thereby precluding causal inferences, are consistent with the notion that prevention strategies targeting modifiable factors and behaviors included in Life's Simple 7, and obesity, in particular, may prevent or delay vascular aging and the associated risk of CVD.

## Acknowledgment

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## Disclosures

G.F. Mitchell is the owner of Cardiovascular Engineering, Inc—a company that develops and manufactures devices to measure vascular

stiffness and serves as a consultant to and receives honoraria from Novartis, Merck, Servier, and Philips.

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## Novelty and Significance

### What Is New?

- Although hypertension and increased vascular stiffness are seen as inevitable parts of the aging process in acculturated societies, these traits are not common in hunter-gatherer populations (although prior studies are limited by the small number of individuals >50 years of age who were studied).
- To elucidate whether the age-related decrease in vascular function is unavoidable, we assessed the prevalence, correlates, and prognosis of healthy vascular aging (HVA) in a Western community-dwelling cohort.

### What Is Relevant?

- The prevalence of HVA, defined as absence of hypertension and pulse wave velocity <7.6 m/s, decreased from 30% in people aged 50 to 59 to 1% in those aged ≥70 years.

- Lower body mass index, absence of diabetes mellitus, and a higher American Heart Association's Life's Simple 7 score were the strongest modifiable correlates of HVA.
- HVA was associated with a 55% lower multivariable-adjusted risk for cardiovascular disease relative to absence of HVA.

### Summary

Although HVA is achievable in individuals acculturated to a Western lifestyle, our results demonstrate that maintaining normal vascular function beyond age 70 is extremely challenging. Our observational data are consistent with the notion that prevention strategies targeting modifiable factors and behaviors included in Life's Simple 7, and obesity, in particular, may prevent or delay vascular aging and the associated risk of cardiovascular disease.



## Prevalence, Correlates, and Prognosis of Healthy Vascular Aging in a Western Community-Dwelling Cohort: The Framingham Heart Study

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## ONLINE SUPPLEMENT

### PREVALENCE, CORRELATES, AND PROGNOSIS OF HEALTHY VASCULAR AGING IN A WESTERN COMMUNITY-DWELLING COHORT: THE FRAMINGHAM HEART STUDY

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## Supplemental Methods

To characterize individuals with and without healthy vascular aging in more detail beyond traditional risk factors, we determined age- and sex-adjusted mean biomarker levels in 1418–3190 individuals with such data available. The methods for determining serum high sensitivity C-reactive protein,<sup>1,2</sup> serum interleukin-6,<sup>1,2</sup> estimated glomerular filtration rate,<sup>3,4</sup> homeostatic model assessment insulin resistance index (HOMA-IR),<sup>5</sup> and urine albumin:creatinine ratio<sup>6</sup> have been previously described in more detail. In addition, we created a genetic risk score for coronary heart disease by multiplying the risk allele count of 58 single nucleotide polymorphisms by the effect size estimated in published genome-wide and exome-wide association studies.<sup>7</sup>

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**Table S1.** Definition of Cardiovascular Health Score.

Goal	Ideal Cardiovascular Health Definition
Current smoking	Never or quit >12 months ago
Body mass index	<25 kg/m <sup>2</sup>
Physical activity	Physical activity index ≥75th percentile
Healthy diet score*	≥2 components
Serum total cholesterol	<200 mg/dL (<2.3 mmol/L) and not on lipid control treatment
Fasting plasma glucose	<100 mg/dL (<5.5 mmol/L) and not on antidiabetic treatment

\*Adapted from Lloyd-Jones et al.<sup>23</sup> – ideal diet score was defined having ≥2 of the following components: ≥4.5 cups/day fruits and vegetables, ≥2x3.5 oz servings/week of fish, ≥3x1 oz servings/day of fiber-rich whole grains, <1500 mg/d of sodium, and <36 oz/week of sugar sweet beverages.

**Table S2.** Characteristics of Included and Excluded Participants.

Characteristic	Included ( <i>n</i> =3196)	Excluded ( <i>n</i> =781)
Cohort		
Offspring	2662 (83.3)	709 (90.1)
Third Generation	534 (16.7)	72 (9.2)
Age, y	61.6±8.6	67.8±9.7
Women	1792 (56.1)	355 (45.5)
Systolic BP, mmHg	127.0±18.0	131±19*
Diastolic BP, mmHg	74.9±9.7	72±11*
PWV, m/s	9.8±3.2	11.9±4.5*
HTN Medication	1103 (34.5)	525 (67.3)*
BMI, kg/m <sup>2</sup>	27.7±5.1	29.9±6.1*
Diabetes mellitus	289 (9.0)	182 (28.4)*
Current Smoker	358 (11.2)	103 (13.2)
Cholesterol, mmol/l	5.2±0.9	4.7±1.0*
HDL cholesterol, mmol/l	1.0±0.2	1.0±0.2*
Lipid-lowering medication	776 (24.3)	419 (53.7)*
Physical activity index	37.8±6.5*	37.4±6.7*
Total caloric intake, kcal/d	1865±650*	1789±606*

Data are shown as mean±SD for continuous variables and as *n* (%) for categorical variables. HVA, healthy vascular aging; BP, blood pressure; PWV, pulse wave velocity; HTN, hypertension; BMI, body mass index; HDL, high density lipoprotein. Asterisk indicates missing data.

**Table S3.** Age- and Sex-Adjusted Means for Genetic, Inflammatory, Renal, and Metabolic Biomarkers According to Healthy Vascular Aging Status.

Characteristic	HVA		No HVA		P-value
	<i>n</i>	Mean	<i>n</i>	Mean	
Genetic CAD score	524	5.74	2401	5.75	0.81
hsCRP, mg/L	563	2.17	2626	3.78	<0.001
IL-6, pg/mL	303	1.81	1115	2.48	<0.001
eGFR, mL/min/1.73m <sup>2</sup>	564	83.6	2626	84.4	0.20
UACR, mg/g	307	10.7	1132	13.0	0.43
Homa-IR	388	3.28	1724	5.41	<0.001

HVA, healthy vascular aging; CAD, coronary artery disease; hsCRP, high sensitivity CRP; IL-6, interleukin-6; eGFR, estimated glomerular filtration rate; UACR, urine albumin:creatinine ratio; homa-IR, homeostatic model assessment of insulin resistance.

**Table S4.** Risk of Cardiovascular Events Related to Healthy Vascular Aging Using 3 Alternate Definitions of Healthy Vascular Aging.

	CVD		Hard CVD	
	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value
HVA Defined as BP <140/90 mmHg and no HTN meds and PWV <8.1 m/s*				
Model 1: Adjusted for sex, age, and cohort	0.52 (0.35–0.75)	<0.001	0.42 (0.25–0.72)	0.002
Model 2: Model 1+BMI, HDL-C, cholesterol, DM, lipid meds, and smoking	0.61 (0.41–0.89)	0.01	0.50 (0.29–0.86)	0.01
Model 3: Model 2+systolic blood pressure	0.69 (0.46–1.02)	0.06	0.62 (0.36–1.08)	0.09
HVA Defined as BP <120/80 mmHg and no HTN meds and PWV <7.6 m/s**				
Model 1: Adjusted for sex, age, and cohort	0.29 (0.14–0.59)	<0.001	0.25 (0.09–0.68)	0.007
Model 2: Model 1+BMI, HDL-C, cholesterol, DM, lipid meds, and smoking	0.36 (0.18–0.74)	0.005	0.32 (0.11–0.87)	0.03
Model 3: Model 2+systolic blood pressure	0.43 (0.21–0.89)	0.02	0.44 (0.16–1.22)	0.11
HVA Defined as BP <140/90 mmHg and no HTN meds and CAC score of 0***				
Model 1: Adjusted for sex, age, and cohort	0.44 (0.20–0.98)	0.04	0.22 (0.05–0.93)	0.04
Model 2: Model 1+BMI, HDL-C, cholesterol, DM, lipid meds, and smoking	0.51 (0.23–1.16)	0.11	0.26 (0.06–1.11)	0.07
Model 3: Model 2+systolic blood pressure	0.54 (0.24–1.23)	0.14	0.31 (0.07–1.36)	0.12

\*772 with HVA (33 CVD events and 16 hard CVD events) and 2424 with no HVA (358 CVD events and 190 hard CVD events).

\*\*380 with HVA (8 CVD events and 4 hard CVD events) and 2816 with no HVA (383 CVD events and 202 hard CVD events). \*\*\*323

with HVA (7 CVD events and 2 hard CVD events) and 1,009 with no HVA (81 CVD events and 40 hard CVD events). CVD, cardiovascular disease; HR, hazard ratio; CI, confidence interval; HVA, healthy vascular aging; BP, blood pressure; HTN, hypertension; PWV, pulse wave velocity; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; DM, diabetes mellitus.

**Figure S1.** Flowchart of Study Participants. CVD, cardiovascular disease; HVA, healthy vascular aging; CAC, coronary artery calcium.

