

Elevated Aortic Pulse Wave Velocity, a Marker of Arterial Stiffness, Predicts Cardiovascular Events in Well-Functioning Older Adults

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Background—Aging results in vascular stiffening and an increase in the velocity of the pressure wave as it travels down the aorta. Increased aortic pulse wave velocity (aPWV) has been associated with mortality in clinical but not general populations. The objective of this investigation was to determine whether aPWV is associated with total and cardiovascular (CV) mortality and CV events in a community-dwelling sample of older adults.

Methods and Results—aPWV was measured at baseline in 2488 participants from the Health, Aging and Body Composition (Health ABC) study. Vital status, cause of death and coronary heart disease (CHD), stroke, and congestive heart failure were determined from medical records. Over 4.6 years, 265 deaths occurred, 111 as a result of cardiovascular causes. There were 341 CHD events, 94 stroke events, and 181 cases of congestive heart failure. Results are presented by quartiles because of a threshold effect between the first and second aPWV quartiles. Higher aPWV was associated with both total mortality (relative risk, 1.5, 1.6, and 1.7 for aPWV quartiles 2, 3, and 4 versus 1; $P=0.019$) and cardiovascular mortality (relative risk, 2.1, 3.0, and 2.3 for quartiles 2, 3, and 4 versus 1; $P=0.004$). aPWV quartile was also significantly associated with CHD ($P=0.007$) and stroke ($P=0.001$). These associations remained after adjustment for age, gender, race, systolic blood pressure, known CV disease, and other variables related to events.

Conclusions—Among generally healthy, community-dwelling older adults, aPWV, a marker of arterial stiffness, is associated with higher CV mortality, CHD, and stroke. (*Circulation*. 2005;111:3384-3390.)

Key Words: aging ■ elasticity ■ epidemiology ■ mortality ■ risk factors

Aging of the arterial system is accompanied by structural changes, including fragmentation and degeneration of elastin, increases in collagen, thickening of the arterial wall, and progressive dilation of the arteries.^{1,2} These changes result in a gradual stiffening of the vasculature and an increase in the velocity of the pressure wave as it travels down the aorta. In a normal elastic aorta, the pressure wave reflects from the periphery and returns to the heart during diastole. This reflected wave helps augment pressure during diastole, which is when coronary blood flow occurs. As the aorta stiffens, the velocity of the pressure wave increases, and the reflected pressure wave eventually reaches the heart at systole instead of diastole, causing augmentation of the systolic blood pressure (SBP) and increased cardiac afterload. The diminished elastic recoil of the stiff aorta, combined with the absence of diastolic augmentation from the reflected

pressure wave, has the potential to reduce coronary filling. Arterial stiffening is associated with a widened pulse pressure that eventually progresses to isolated systolic hypertension, a condition affecting 30% of adults by the time they reach 80 years of age.³

Among high-risk clinical populations, elevated arterial stiffening is associated with increased mortality. Among persons with end-stage renal disease, both the incremental elastic modulus evaluated in the common carotid artery⁴ and aortic pulse wave velocity (aPWV)⁵ have been found to predict mortality. Among hypertensive individuals, aPWV was found to be an independent predictor of cardiovascular and all-cause mortality.⁶ Finally, in a small study of hospitalized older adults, elevated aPWV was shown to predict cardiovascular death.⁷ To date, no longitudinal study has examined whether noninvasive measures of arterial stiffness

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are associated with mortality in the general population. The purpose of the present study was to determine the association between increased central arterial stiffening and mortality and cardiovascular (CV) events in a general cohort of well-functioning, community-dwelling older adults.

Methods

Study Sample

The Health, Aging, and Body Composition (Health ABC) study is a community-based prospective study of the impact of changes in weight and body composition on age-related physiological and functional changes. Participants (age 70 to 79 years) were recruited from March 1997 to July 1998 at 2 field centers in Pittsburgh, Pa, and Memphis, Tenn. Participants were drawn from a random sample of Medicare beneficiaries residing in zip codes from the metropolitan areas surrounding Pittsburgh and Memphis. Eligible participants reported no difficulty walking one quarter of a mile, climbing 10 steps, or performing basic activities of daily living. Participants also had to be free of life-threatening illness and planned to remain in the area for ≥ 3 years. The cohort consists of 1491 men (48.5%) and 1584 women (51.5%), of whom 41.7% are black. PWV data are missing for 354 participants because of equipment problems; 233 patients had waveforms that were unusable because there was no clearly defined initial upstroke of the waveform, the trace was contaminated with a large venous flow component, no consistent flow waveform was found, or the ECG timing signal used to synchronize waveform averaging was too noisy for reliable use. This report is based on the remaining 2488 participants. There were small differences between participants with available versus missing aPWV measures. Those with missing aPWV measures were more often black (47% versus 40%) and had lower blood pressures (134 versus 136 mm Hg SBP), higher heart rates (67 versus 65 bpm), and lower cholesterol (199 versus 204 mg/dL). All participants signed a written informed consent form that was approved by the institutional review boards of the University of Pittsburgh and University of Tennessee.

Prevalent medical conditions were evaluated by questionnaire and confirmed by use of specific medications or procedures. Prevalent CV disease (CVD) included myocardial infarction, angina, stroke, or transient cerebral ischemia or any revascularization procedure, including endarterectomy or angioplasty.

aPWV Methods

aPWV can be measured noninvasively,⁸ and the technique has been found to be highly reproducible, with replicate testing yielding an intraclass correlation >0.80 .⁹ aPWV was measured from simultaneous Doppler flow signals obtained from the right carotid and right femoral arteries with nondirectional transcutaneous Doppler flow probes (model 810A, 9.0- to 10-MHz probes, Parks Medical Electronics, Inc). Digitized data were recorded by custom programming for subsequent analysis. A minimum of 10 beats were averaged for each simultaneous recording site using the QRS for synchronization. Three separate runs were recorded for each participant, and all usable runs were averaged. The distance between the carotid and femoral sampling sites was measured above the surface of the body with a metal tape measure. This was done to avoid overestimation of the distance portion of the aPWV equation. The time differentials between the onset of flow at carotid and femoral (defined as foot of the pressure tracing at each site) sites were divided by the associated distance to produce flow velocity. Stiffer vessels are associated with a faster PWV. The National Institute on Aging, Laboratory of Cardiovascular Science, Gerontology Research Center (Baltimore, Md) trained and certified all study personnel before data collection, read the wave forms, and evaluated data quality. Results from all acceptable runs were averaged for the final PWV measure used in the analyses. Replicate measures of aPWV in 14 subjects revealed intraclass correlations of 0.88 between sonographers and 0.84 between readers.

Ankle blood pressures were used as a measure of occlusive disease to the lower extremities. Pressures were taken in the right arm and both ankles (posterior tibial artery) with standard blood pressure cuffs and a pencil Doppler. The SBP of the ankle was divided by the SBP of the arm to create the ankle/arm index. Measures were done twice, and the results were averaged. The lower value between the 2 legs was used, and an ankle/arm index of ≤ 0.90 was considered evidence of occlusive disease.

Laboratory Values

Fasting blood samples were obtained for assay. HDL, triglycerides, and glucose were assayed with a colorimetric technique on a Johnson and Johnson Vitros 950 analyzer. HDL was assayed after a magnetic precipitation of LDL, VLDL, and chylomicrons. LDL was estimated with the Friedewald equation.¹³ Insulin was assayed with a micro-particle enzyme immunoassay (Abbott IMx analyzer); for hemoglobin A_{1c}, ion-exchange high-performance liquid chromatography was used (Biorad Variant analyzer). Creatinine values of 132.6 $\mu\text{mol/L}$ (1.5 mg/dL) for men and $\geq 115 \mu\text{mol/L}$ (1.3 mg/dL) for women were considered elevated.

Participant Follow-Up and CV Events

Participants were contacted every 6 months, alternating clinic visits and phone interviews. Vital status, functional limitations, all hospitalizations, and selected outpatient events were ascertained. Date of death was verified, and deaths were reviewed for immediate and underlying cause through death certificates, hospital records, and a proxy interview. Cause of death was assigned by a committee made up of 4 to 6 Health ABC investigators who are clinicians.

In addition to evaluating the association between baseline aPWV and total mortality, we also evaluated deaths from CVD. CVD deaths included atherosclerotic CVD (definite fatal myocardial infarction, definite fatal coronary heart disease [CHD], or possible fatal CHD), stroke, atherosclerotic disease other than coronary or cerebrovascular, and other CVD (eg, valvular heart disease). Additional cardiovascular outcomes were as follows: incident CHD, defined by coronary death or any overnight hospitalization in an acute care hospital for acute myocardial infarction or angina; stroke, defined as fatal and nonfatal stroke events; and congestive heart failure (CHF), defined as any overnight hospitalization in an acute care hospital for CHF during the follow-up. Follow-up time was calculated as months between the first clinic visit and date of event or date of last follow-up for censored participants.

Statistical Methods

aPWV was examined using sex-specific quartiles, with the lowest quartile serving as the reference category. The Kaplan-Meier method was used to estimate unadjusted survival curves for the 4 aPWV groups. The log-rank test was used to compare the unadjusted survival curves. The Kaplan Meier survival curves indicated a threshold effect between quartiles 1 and 2, particularly in relation to CV events. Thus, the primary analysis is presented with aPWV divided into sex-specific quartiles, with each upper quartile using the lowest quartile as a reference value. Quartile definitions for men were as follows: quartile 1, 317.0 to 657.0 cm/s; quartile 2, 657.5 to 838.0 cm/s; quartile 3, 841.0 to 1085.0 cm/s; and quartile 4, 1085.5 to 2926.0 cm/s. For women, the definitions were as follows: quartile 1: 312.0 to 627.0 cm/s; quartile 2, 628.7 to 786.7 cm/s; quartile 3, 787.0 to 1018.0 cm/s; and quartile 4, 1019.5 to 2998.0 cm/s.

After assessing the proportionality assumption, we used the Cox proportional-hazards model¹⁰ to assess the association between aPWV quartile and study outcomes. Hazard ratios (relative risk) and 95% CIs are reported. All variables related to either aPWV or an outcome measure were considered in the multivariate analysis. Adjustment was done sequentially, starting with age, gender, race, SBP, and site. Next, other variables found to be independently predictive of ≥ 1 event were added (baseline evidence of CVD, creatinine, cholesterol). "Independently predictive" here means that the partial regression coefficients remained statistically significant with the other variables in the model. Additional variables related to

TABLE 1. Baseline Characteristics by Sex-Specific aPWV Quartiles

	aPWV Quartile				Total (n=2488)	P	
	1 (n=622)	2 (n=620)	3 (n=625)	4 (n=621)		Difference By aPWV Quartile	Age Adjusted
Gender							
Male	296 (47.6)	296 (67.7)	298 (47.7)	296 (47.7)	1186 (47.7)		
Female	326 (52.4)	324 (52.3)	327 (52.3)	325 (52.3)	1302 (52.3)		
Race							
Black	214 (34.4)	244 (39.4)	263 (62.1)	281 (65.3)	1002 (40.3)	0.001	<0.001
White	408 (65.6)	376 (60.0)	362 (57.9)	340 (56.7)	1486 (59.7)		
Smoking							
Never	303 (48.7)	277 (44.7)	247 (39.7)	268 (43.2)	1095 (44.1)	0.08	0.03
Former	262 (42.1)	279 (45.0)	311 (50.0)	284 (45.7)	1136 (45.7)		
Current	57 (9.2)	64 (10.3)	64 (10.3)	69 (11.1)	254 (10.2)		
High creatinine							
Yes	31 (5.0)	46 (7.5)	58 (9.4)	56 (9.0)	191 (7.7)	0.02	0.01
Walking and exercise, kcal/wk							
<200	154 (24.8)	224 (36.1)	219 (35.0)	257 (41.4)	854 (34.3)	<0.001	<0.001
200–600	141 (22.7)	129 (20.8)	140 (22.4)	121 (19.5)	531 (21.3)		
600–1500	164 (26.4)	138 (22.3)	146 (23.4)	133 (21.4)	581 (23.4)		
>1500	163 (26.2)	129 (20.8)	120 (19.2)	110 (17.7)	522 (21.0)		
Prevalent CVD	141 (22.7)	129 (20.8)	190 (30.4)	182 (29.3)	642 (25.8)	<0.001	<0.001
History of hypertension	236 (38.3)	294 (47.7)	334 (54.1)	388 (62.9)	1252 (50.7)	<0.001	<0.001
History of diabetes	52 (8.4)	73 (11.8)	109 (17.4)	128 (20.7)	362 (14.6)	<0.001	<0.001
Ankle/arm index \leq 0.90	53 (8.9)	68 (11.5)	93 (15.6)	110 (19.3)	324 (13.8)	<0.001	<0.001
Age, y	73.4 \pm 2.8	73.6 \pm 2.8	73.9 \pm 3.0	73.9 \pm 2.8	73.7 \pm 2.9	<0.001	
SBP, mm Hg	130.9 \pm 19.0	134.0 \pm 19.3	138.4 \pm 20.9	142.4 \pm 21.8	136.4 \pm 20.7	<0.001	<0.001
Diastolic blood pressure, mm Hg	70.8 \pm 10.9	71.7 \pm 11.0	72.1 \pm 11.8	72.9 \pm 12.2	71.9 \pm 11.5	0.02	0.02
Pulse pressure, mm Hg	60.0 \pm 16.0	62.3 \pm 16.4	66.3 \pm 17.9	69.5 \pm 18.7	64.5 \pm 17.7	<0.001	<0.001
Heart rate, bpm	61.9 \pm 9.9	64.9 \pm 11.0	66.2 \pm 11.3	67.4 \pm 11.7	65.0 \pm 11.3	<0.001	<0.001
Hemoglobin A _{1c} *	6.0	6.1	6.1	6.2	6.1	<0.001	<0.001†
Cholesterol, mmol/L	5.2 \pm 0.9	5.3 \pm 1.0	5.3 \pm 1.1	5.3 \pm 1.0	5.28 \pm 1.0	0.52	0.43
Body mass index, kg/m ²	26.2 \pm 4.5	27.6 \pm 4.6	28.1 \pm 5.0	27.7 \pm 5.0	27.4 \pm 4.8	<0.001	<0.001

Values are n (%) or mean \pm SD.

*Median given because hemoglobin A_{1c} was skewed.

†Age-adjusted probability value obtained using log-transformed hemoglobin A_{1c}.

events but also highly correlated with aPWV were added next (smoking, physical activity, and hemoglobin A_{1c}). Because increases in heart rate may be part of the causal pathway linking aPWV to CV outcomes, there is disagreement as to whether it should be included in models such as those presented here. Thus, heart rate was added separately, allowing the results to be viewed both with and without this covariate. Finally, to determine whether the effect of aPWV on outcome was separate from other measures of subclinical disease, the presence or absence of a low ankle blood pressure was added. A value of $P \leq 0.05$ was considered statistically significant. SAS version 8.0 for Windows was used for all analyses.¹¹

Results

aPWV was available for 2488 of the 3075 Health ABC participants. Men make up 48% of this group, and 40% were black. At baseline, the average age of participants was 74 years (SD, 3 years), and aPWV values ranged from 312 to 2998 cm/s, with a mean of 903 cm/s (SD, 394 cm/s) and median of 810 cm/s (interquartile range, 641 to 1052 cm/s).

Other population characteristics can be found in Table 1. Previous publications from Health ABC have reported significant associations between aPWV and age, black race, SBP, heart rate, weight, body fat, smoking, hemoglobin A_{1c}, history of diabetes, history of hypertension,¹² and physical activity.¹³ Table 1 shows that these variables are also related to aPWV quartile.

Over an average follow-up of 4.6 years, 265 deaths occurred. Of these, 111 were from cardiovascular causes. There were 341 CHD events, 94 stroke events, and 181 cases of CHF.

Initially, outcome analyses were run with aPWV as a continuous variable, and significant associations were found between higher aPWV and each of the outcomes evaluated. (Odds ratios per unit of log[*pwv*] were 1.6 [95% CI, 1.2 to 2.2] for total mortality, 1.8 [95% CI, 1.1 to 2.8] for CV mortality, 1.4 [95% CI, 1.1 to 1.8] for CHD, 2.0 [95% CI, 1.2

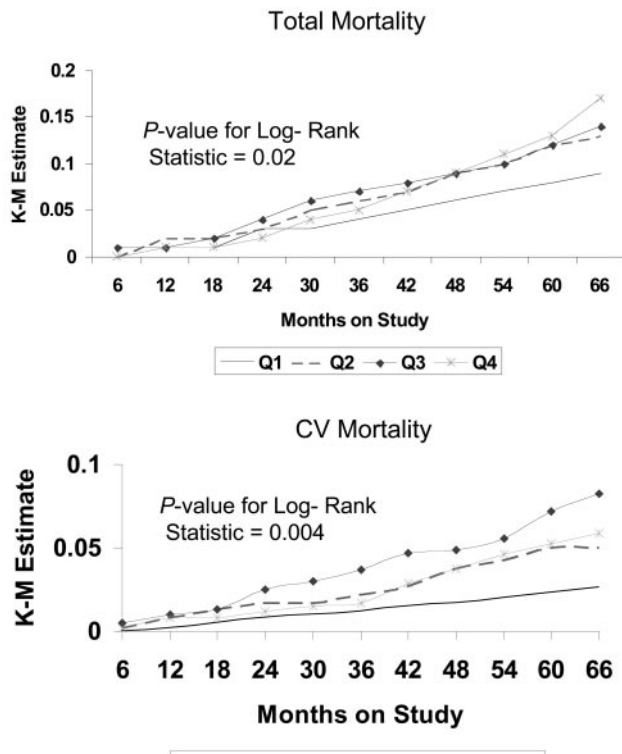


Figure 1. Kaplan-Meier estimates of total mortality (top) and CV mortality (bottom) by aPWV quartile.

to 3.2] for stroke, and 1.5 [95% CI, 1.0 to 2.1] for CHF; $P < 0.05$ for all.) When the variable was divided into sex-specific quartiles for purposes of graphic presentation, log-rank tests comparing pairs of Kaplan-Meier survival curves indicated a threshold effect between the first and second quartiles for each outcome ($P = 0.024$ for total mortality, $P = 0.019$ for CV mortality, $P = 0.016$ for CHD, and $P = 0.001$ for stroke). Thus, remaining analyses focused on aPWV quartile. Higher aPWV was positively associated with total mortality (Figure 1, top; $P = 0.019$ for the log-rank statistic). Compared with the lowest aPWV quartile, the relative risks of mortality were 1.5 (95% CI, 1.1 to 2.2), 1.6 (95% CI, 1.1 to 2.3), and 1.7 (95% CI, 1.2 to 2.5) for the second, third, and fourth quartiles, respectively (Table 2). CV mortality also showed a strong association with aPWV quartile (Figure 1, bottom; $P = 0.004$ for the log-rank statistic). Compared with the lowest aPWV quartile, the relative risk of a cardiovascular death was >2 for each of the 3 top quartiles (Table 2). This association remained significant when the 642 participants with prevalent CVD at baseline were excluded ($P = 0.018$). Non-CV deaths were not associated with aPWV (relative risk, 1.3 [95% CI, 0.8 to 2.0], 1.0 [95% CI, 0.6 to 1.6], and 1.5 [95% CI, 1.0 to 2.3] for the second, third, and fourth quartiles, respectively).

In evaluations of CV events, aPWV quartile was significantly associated with CHD ($P = 0.007$) and stroke ($P < 0.001$) but not CHF ($P = 0.328$) (Figure 2 and Table 2).

Each of the variables in Table 1 was considered in multivariate analysis; this list includes variables associated with any of the outcomes presented here. Because many of

these variables are highly correlated, only those independently associated (remaining significant after controlling for other covariates) with one of the outcomes were included in the final multivariate models. After adjustment for age, gender, race, and SBP, aPWV remained significantly associated with all end points except CHF. Next, prevalent CVD, creatinine, and cholesterol were added. These additional adjustments had relatively little effect on the end points of CHD, stroke, and CV death, whereas the association between aPWV and total mortality diminished somewhat. When mean arterial pressure or pulse pressure was used in place of SBP, there was very little difference in the results. Smoking, physical activity, and hemoglobin A_{1c}, 3 variables highly correlated with aPWV were next added, and this also produced relatively little change in the association. The addition of heart rate, which may be involved in the pathway linking aPWV to events, had relatively little effect on the end points of CHD, stroke, and CV death. However, aPWV was no longer significantly related to total mortality. A final consideration was whether aPWV, a measure of arterial stiffening, predicts outcome separately from a measure of subclinical atherosclerosis. Thus, the presence or absence an ankle-to-arm SBP ratio (ankle/arm index) of ≤ 0.90 was added. This also did not diminish the strength of the association between aPWV and CV events.

Discussion

These data demonstrate that aPWV, a marker of arterial stiffness, is associated with CHD, stroke, and CV mortality in a well-functioning, community-dwelling population sample. Independent of age, gender, race, and SBP, subjects with aPWV values >641 cm/s for men and 627 cm/s for women (the 25th percentile of the aPWV distribution) had a >2 -fold increase in the risk of CVD, a 2- to 3-fold increase in stroke, and a $>50\%$ increase in CHD events compared with those with values below this level. In younger populations of men, elevated pulse pressure, the blood pressure parameter most closely associated with arterial stiffening, has been associated with mortality.^{14–16} Thus, it is likely that vascular stiffness will eventually be found to be associated with CV end points in younger populations as well. Independent of chronological age, increased aPWV is likely a marker of the health of the vascular system.

It was somewhat surprising that aPWV was not found to be associated with CHF. Although the observed trend of the association was similar to the other CV events, the association was clearly weaker and did not hold up in multivariate analysis. This study had 80% power to detect a relative risk of 1.51 when each upper quartile was compared with quartile 1. Thus, power does not appear to be the issue. The increased afterload that accompanies the early reflected pressure wave in the setting of vascular stiffening is hypothesized to result in increases in left ventricular mass and eventually CHF. However, the literature has been inconsistent in demonstrating this. Although pulse pressure has consistently been found to be associated with CHF,^{17–19} the association between vascular stiffness measures and CHF has been inconsistent. In the Cardiovascular Health Study, among hypertensive patients, concentric left ventricular hypertrophy has been linked to

TABLE 2. Unadjusted & Adjusted Associations Between Sex-Specific aPWV and Events

	Mortality				CV Events					
	Total (n=265)		CV (n=111)		CHD (n=341)		Stroke (n=94)		CHF (n=181)	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Unadjusted										
Q1	1.00	...	1.00	...	1.00	...	1.00	...	1.00	...
Q2	1.54*	1.06–2.22	2.14*	1.13–4.07	1.51*	1.09–2.09	3.16†	1.55–6.47	1.33	0.86–2.06
Q3	1.57*	1.09–2.27	3.00†	1.63–5.53	1.73†	1.26–2.37	2.08	0.97–4.44	1.41	0.92–2.17
Q4	1.74†	1.21–2.49	2.30*	1.22–4.34	1.54†	1.12–2.13	3.56†	1.76–7.22	1.45	0.94–2.22
Adjusted for age, gender, race, SBP, and site										
Q1	1.00	...	1.00	...	1.00	...	1.00	...	1.00	...
Q2	1.47*	1.02–2.14	1.99*	1.04–3.80	1.52*	1.09–2.11	3.06†	1.49–6.28	1.33	0.86–2.06
Q3	1.47*	1.00–2.15	2.66†	1.42–5.00	1.77†	1.28–2.46	1.92	0.88–4.16	1.40	0.90–2.19
Q4	1.60*	1.10–2.32	1.98*	1.03–3.81	1.53*	1.09–2.13	3.21†	1.56–6.63	1.35	0.87–2.10
Adjusted for above plus prevalent CVD, creatinine, and cholesterol										
Q1	1.00	...	1.00	...	1.00	...	1.00	...	1.00	...
Q2	1.52*	1.04–2.22	2.12*	1.09–4.11	1.57†	1.13–2.19	2.97†	1.44–6.13	1.27	0.82–1.99
Q3	1.41	0.95–2.08	2.49†	1.30–4.77	1.63†	1.17–2.28	1.77	0.81–3.84	1.24	0.79–1.94
Q4	1.55*	1.06–2.28	1.89	0.97–3.72	1.42*	1.01–1.99	2.99†	1.45–6.16	1.21	0.78–1.88
Adjusted for above plus smoking, physical activity, and hemoglobin A _{1c}										
Q1	1.00	...	1.00	...	1.00	...	1.00	...	1.00	...
Q2	1.45	0.99–2.12	2.06*	1.06–4.00	1.55*	1.11–2.16	2.80†	1.36–5.79	1.18	0.75–1.84
Q3	1.25	0.84–1.86	2.16*	1.11–4.19	1.51*	1.08–2.13	1.62	0.74–3.53	1.10	0.63–1.60
Q4	1.32	0.89–1.96	1.56	0.78–3.12	1.32	0.93–1.87	2.76†	1.33–5.74	0.98	0.62–1.54
Adjusted for above plus heart rate										
Q1	1.00	...	1.00	...	1.00*	...	1.00	...	1.00	...
Q2	1.39	0.95–2.04	1.95*	1.00–3.80	1.53*	1.10–2.15	2.77†	1.34–5.74	1.12	0.72–1.75
Q3	1.18	0.79–1.76	2.02*	1.04–3.93	1.50*	1.07–2.11	1.59	0.72–3.48	0.91	0.57–1.46
Q4	1.21	0.81–1.81	1.41	0.70–2.84	1.29	0.91–1.84	2.69†	1.29–5.62	0.87	0.55–1.38
Adjusted for above plus ankle/arm index										
Q1	1.00	...	1.00	...	1.00	...	1.00	...	1.00	...
Q2	1.45	0.98–2.16	2.13*	1.07–4.24	1.48*	1.05–2.09	2.93†	1.37–6.27	0.99	0.62–1.58
Q3	1.31	0.87–1.99	2.36*	1.19–4.68	1.45*	1.02–2.05	1.63	0.72–3.70	0.91	0.57–1.47
Q4	1.15	0.76–1.76	1.31	0.62–2.74	1.14	0.79–1.64	2.60*	1.19–5.64	0.75	0.46–1.22

RR indicates relative risk; Q, quartile.

* $P < 0.05$; † $P < 0.01$.

arterial stiffening.²⁰ However, other studies suggest that this association depends on the vascular stiffness measure used.²¹ It is possible that either a survival bias or functional changes that occur with CHF itself interfere with the ability to detect this association. Supporting this idea are recent data reporting that in patients with decompensated CHF, lower pulse pressure is a predictor of poor outcome.²² It should be noted that in the data presented here, pulse pressure was independently associated with CHF even though aPWV was not. A final possibility is that the blood pressure parameters are so overwhelmingly related to CHF that this masks our ability to observe a separate effect of aPWV.

In the older adults studied here, there appeared to be a threshold effect, with elevated CV risk associated primarily with aPWV values in the upper 3 quartiles of the distribution. Because the threshold is so low, one could also say that in

older adults, a low aPWV is protective for CHD, stroke, and CV death. In older adults, a low aPWV may identify individuals who have undergone a “healthy aging” of the CV system. That is, their vasculature has been spared the damaging influence of risk factors that often accompany aging.

The association between aPWV and CV mortality and CV events was independent of heart rate, but the association with total mortality was not. There is debate over whether heart rate should be included in a predictive model such as that used here. Both arterial pressure and heart rate are intrinsically related to the elastic properties of the arteries,^{1,23} and in this context, it is not really appropriate to enter these variables into an analysis in which arterial stiffness is a covariate. However, both heart rate²⁴ and blood pressure are related to cardiovascular outcomes. Thus, to determine whether aPWV has predictive value while controlling for these vascular

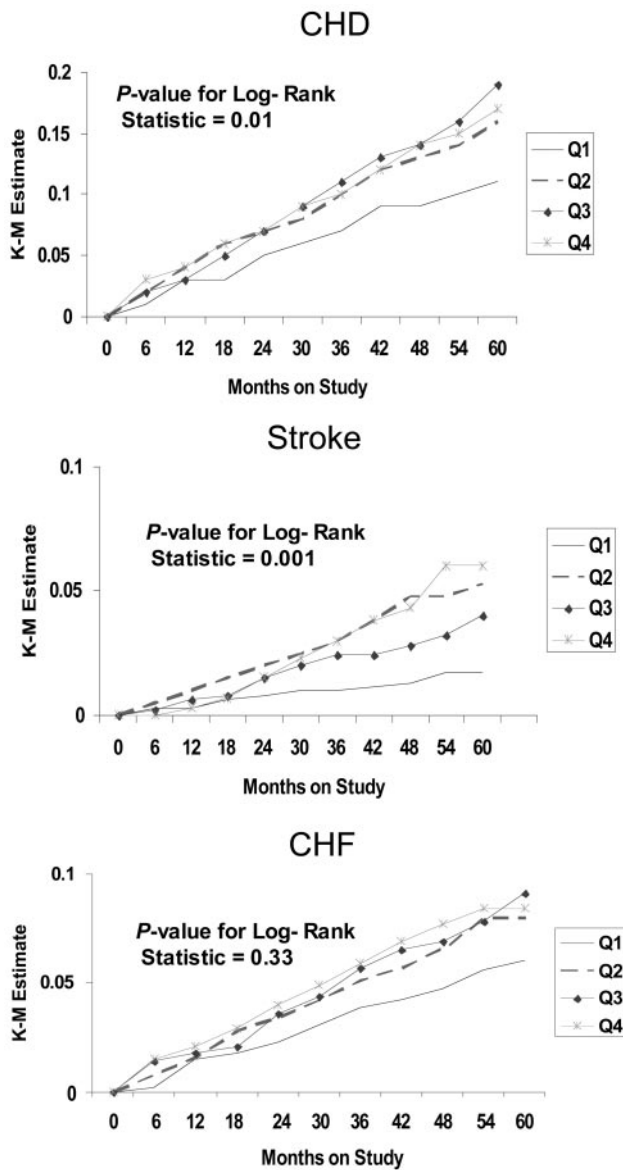


Figure 2. Kaplan-Meier estimates of CHD (top), stroke (middle), and CHF (bottom) by aPWV quartile.

parameters, one can argue to include them. For this reason, the multivariate models were presented both ways.

It has been suggested that the association between vascular stiffness and heart rate may be part of the underlying mechanism through which heart rate is associated with mortality.²⁵ An increased heart rate likely promotes arterial stiffening through exposing the vessel wall to greater cyclic stress. This can cause stiffening through thinning and fragmentation of elastin, particularly in the aorta, which endures the highest pulsatile stress.²⁶ Cyclic stretching may also result in arterial stiffening by stimulating muscle cells to produce matrix component.²⁷ Heart rate has also been shown to predict the progression of aPWV.²⁸ Although it is clear that heart rate and vascular stiffening are intertwined, our data indicate that each has a separate contribution to CV mortality in older adults.

Arterial stiffening is the underlying cause of isolated systolic hypertension.²⁹ The association between isolated

systolic hypertension and increased prevalence of cardiovascular events is well established.³⁰ The findings presented here are consistent with this relationship and suggest that prevention of vascular stiffness will improve the health of older adults. The primary risk factors for vascular stiffness are hypertension^{31–34}; glucose abnormalities, including diabetes,^{35,36} hyperglycemia, hyperinsulinemia, and impaired glucose tolerance^{37–39}; and increased body fat, specifically visceral adipose tissue.^{12,40} In Health ABC participants, we have reported that all markers of central fat, including visceral and intermuscular and intramuscular fat, are associated with a higher PWV.¹² In a related article, we reported that central fat is most strongly related to fasting insulin and glucose in those who are the least overweight.⁴¹ Therefore, although prevention of obesity in middle age would likely serve to prevent the progression of arterial stiffening seen with aging and with diabetes, strategies to prevent the shift to central adiposity may have the greatest impact. This can be accomplished through increased physical activity. In the Health ABC population, we have found cross-sectionally that greater physical activity is associated with lower vascular stiffness, and we have hypothesized that this benefit is through the prevention of central adiposity and insulin resistance.¹³ This is consistent with the fact that among populations with high physical activity, the increase in blood pressure with age is not seen.^{42,43}

Although the demonstration of an association between arterial stiffness and CV events is significant, other end points potentially affected by arterial stiffness may have a broader public health impact. The fact that increased aPWV was strongly predictive of stroke suggests that there may also be an association between aPWV and cognitive function. An analysis of these data in Health ABC is currently underway. The broader literature has shown that treating systolic hypertension has positive effects on heart failure⁴⁴ and measures of daily life activity⁴⁵ and a reduced incidence of dementia.⁴⁶ Thus, a better quality of life may turn out to be the overriding benefit of healthy vascular aging.

In conclusion, greater aPWV is associated with higher CV mortality, CHD events, and stroke among community-dwelling, well-functioning older adults. Efforts to prevent age-associated arterial stiffening will likely improve the health of older adults.

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