

Weight Change Is Associated With Change in Arterial Stiffness Among Healthy Young Adults

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Abstract—Risk factors for arterial stiffness progression have not been well characterized. We examined the relationship between arterial stiffness progression and body weight and weight gain in a group of healthy young adults. Aortic pulse-wave velocity was assessed at 2 time points approximately 2 years apart in 152 white and black adults aged 20 to 40 years, and was standardized by the time between visits to obtain annualized pulse-wave velocity changes. Blacks had 15.5 cm/s per year larger annual pulse-wave velocity increases compared with whites ($P=0.02$), even after multivariable adjustment for weight and blood pressure changes. Larger annual pulse-wave velocity increases were also associated with larger baseline body weight ($P=0.02$), waist girth ($P=0.003$), and body mass index ($P<0.001$), and greater annual weight gain ($P=0.02$), after adjustment for baseline pulse-wave velocity. After multivariable adjustment that included blood pressure changes, larger baseline waist girth ($P=0.009$), baseline body mass index ($P=0.001$), body mass index increase ($P=0.037$), and weight gain ($P=0.017$) remained significantly associated with larger annual pulse-wave velocity progression. Weight change showed a direct relationship with pulse-wave velocity change; mean annual pulse-wave velocity changes were -29.9 cm/s per year (regression) for those with ≥ 4.5 kg annual weight loss and 18.2 cm/s per year (progression) for those with ≥ 4.5 kg annual weight gain. These data show strong associations between weight gain and arterial stiffness progression, as well as between weight loss and arterial stiffness regression. These data greatly underscore the vascular benefit of weight loss. Successful weight loss programs in young adults, particularly blacks, are needed. (*Hypertension*. 2005;45:187-192.)

Key Words: arteriosclerosis ■ obesity ■ elasticity ■ blacks

Obesity is an increasing public health problem in the United States among adults and children,^{1,2} and it has been shown to increase the risk for stroke, incident cardiovascular disease, cardiovascular mortality, and all-cause mortality among middle-aged and elderly participants in longitudinal studies.³⁻⁶ Additionally, excess weight is associated with numerous cardiovascular risk factors such as hypertension, dyslipidemia, type 2 diabetes, and the metabolic syndrome.^{7,8}

Obesity may also be associated with early vascular changes. There are numerous techniques for assessing the early stages of vascular disease. One such technique, aortic pulse-wave velocity, involves quantifying the amount of arterial stiffening and can be thought of as a measure of premature vascular aging.⁹ Arterial stiffening has been associated with other measures of subclinical vascular disease, as well as with cardiovascular mortality.¹⁰⁻¹⁴ In line with the associations between excess weight and cardiovascular risk factors, morbidity, and mortality, we have previously shown that excess weight appears to have vascular effects in individuals as young as 20 to 25 years, with overweight and obese

individuals having significantly stiffer arteries than normal-weight individuals in cross-sectional analyses.¹⁵ Whether changes in weight are associated with progression of arterial stiffness has not yet been explored. Only 1 published study to the authors' knowledge has assessed determinants of progression of arterial stiffness, and this study assessed associations between 6-year arterial stiffness progression and baseline cardiovascular risk factors in a primarily middle-aged population.¹⁶

The purpose of the current study was to assess the relationship between changes in arterial stiffness and changes in weight, body mass index, and waist circumference among healthy young adults over a 2-year period.

Methods

Study Population

Arterial stiffness was assessed at baseline in 196 participants aged 20 to 40 years, and ≈ 2 years later in 163 participants (83% follow-up rate). Participants were recruited from the general population of Allegheny County, Pennsylvania as previously published.¹⁵ Exclusion criteria at baseline included use of antihypertensive, lipid-

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lowering, thyroid, blood sugar-lowering, or cardiovascular medications, as well as a history of lupus or clinical cardiovascular disease. However, participants could initiate medication use subsequent to the baseline visit ($n=6$). This study was approved by the University of Pittsburgh's Institutional Review Board and all participants provided written informed consent before initiation of the study protocol.

Ultrasound Measurements

Arterial stiffness was measured via aortic pulse-wave velocity (aPWV) after ≈ 30 minutes of supine rest, using Doppler ultrasound of the right carotid and femoral arteries. The time portion of the velocity equation was taken as the time differential between simultaneously collected carotid and femoral wave forms, using the R-wave of the EKG for synchronization. A minimum of 7 beats were averaged for each simultaneous recording site. 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 using a metal tape measure. The time between the onset of flow (the foot of the waveform) at the carotid site and the onset of flow at the femoral site was divided by the associated carotid to femoral distance to produce flow velocity.

Sonographers were certified on study protocols yearly and participated in several continuous quality control assessment processes on a monthly and a quarterly basis to maintain high-quality scans. To examine aPWV reproducibility, aPWV measures were performed on 9 participants of the current study by 2 technologists, on 2 visits, ≈ 1 week apart. The intraclass correlation coefficient was calculated; this statistic represents the proportion of the total variance caused by within-person variability and ranges from 0 to 1, with values approaching 0 indicating little within-person variability and large between-person and technologist variability, and values approaching 1 indicating large within-person variability and little between-person and technologist variability. The intraclass correlation coefficient for the current study was 0.78, indicating excellent reproducibility.¹⁷ Similar aPWV reproducibility results have previously been demonstrated for this ultrasound laboratory.¹⁸

Anthropometric, Laboratory, and Demographic Measures

At the baseline and follow-up visits, 2 measurements of weight and waist circumference were averaged. Body mass index was calculated as weight in kg/height in meters squared. Age and current smoking status were assessed by questionnaire at the baseline and follow-up visits. At each ultrasound examination, 3 seated blood pressures were taken after 5 minutes of rest with a standard mercury sphygmomanometer using cuff sizes appropriate to the manufacturer's recommendations. The first measurement was discarded and the second and third measurements were averaged. Pulse pressure was calculated as systolic blood pressure minus diastolic blood pressure. Mean arterial pressure (MAP) was calculated as

$$[(2 \times \text{diastolic blood pressure}) + \text{systolic blood pressure}] / 3$$

Total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, and glucose were determined after a 12-hour fast using standard laboratory procedures at the baseline visit. Laboratory measures were not performed at the follow-up visit.

Statistical Analysis

Of the 163 individuals who returned for the follow-up visit, 152 had useable aPWV values at both baseline and follow-up. Those who did not return for the follow-up visit were more likely to be black. There were no significant differences in age, blood pressure, aPWV, cholesterol, percent male, or percent current smoker at baseline between those who returned for follow-up and those who did not. Additionally, among those who returned for follow-up, there were no significant differences in baseline body weight or follow-up body weight between the 11 individuals who did not have useable aPWV

values and the 152 who did, indicating that a measurement bias related to body habitus was likely not present. To partially account for the effects of aging, aPWV change and changes in covariates over the follow-up period were standardized by the time between visits, creating annualized measures of change. Additionally, multivariable modeling included adjustment for the time between visits. Annual aPWV change was normally distributed. Linear regression was used to estimate the effect of covariates on annual PWV change, adjusting for baseline aPWV. Multivariable linear regression was used to determine if associations between annual aPWV change and both baseline obesity measures and change in obesity measures were independent of important covariates. The possibility of nonlinear associations between obesity measures and aPWV change were examined by inclusion of quadratic and cubic obesity terms in multivariable modeling and by graphical assessment; nonlinear associations were not confirmed. Weight change was categorized into 2.3-kg (5-lb) increments despite small sample sizes in each weight change category, to graphically illustrate the strong association between weight change and aPWV change. General linear modeling least-squares means were used to estimate mean aPWV changes by weight change groupings. The criterion for statistical significance was $P < 0.05$ for all results. SAS version 8.2 software (SAS Institute, Cary, NC) was used for all analyses.

Results

The mean follow-up time was 2.0 years, with a minimum follow-up of 1.3 years and a maximum follow-up of 3.7 years. Annual aPWV change ranged from -147.1 cm/s per year to 194.2 cm/s per year, with negative values indicating a decrease in aPWV over the follow-up period and positive values indicating an increase in aPWV over the follow-up period. Mean values for baseline covariates and annual changes in covariates can be found in Table 1. The mean age of participants was 30.4 years, 45% were male, and 44% were black. Mean systolic blood pressure, diastolic blood pressure, and lipid values were within the normal range.

Blacks had significantly larger annual aPWV increases than whites, even with adjustment for baseline aPWV (Table 2). All 3 baseline obesity measures were positively associated with annual increase in aPWV. Additionally, greater weight gain was significantly associated with larger annual increase in aPWV, while a greater body mass index increase was borderline significantly associated with larger annual increase in aPWV. These associations remained even when adjusted further for baseline weight or body mass index (data not shown). An annual increase in pulse pressure of 5 mm Hg/year was associated with an annual increase in aPWV of 8.7 cm/s per year, because of nonsignificant associations between annual aPWV increases and annual increase in systolic blood pressure and annual decrease in diastolic blood pressure.

Further adjustment for time between visits, race-ethnicity, sex, age, baseline MAP, and change in MAP attenuated associations between annual aPWV change and baseline weight, but annual increase in aPWV remained significantly associated with baseline waist girth, baseline body mass index, and annual weight change (Table 3). Additionally, greater body mass index increase achieved statistical significance after multivariable adjustment. Plots indicated that model residuals for all 3 models were normally distributed with the exception of 1 outlier. When all multivariable regression models were fit excluding this residual outlier, the magnitude of each β coefficient was unchanged from that presented in Table 3, but baseline weight (model 3) achieved

TABLE 1. Baseline Characteristics and Annual Changes in Characteristics of the Study Population

Variable	Mean (SD) or No. (%)
Baseline	
Age, y	30.4 (6.4)
Male, n (%)	69 (45.4)
Black, n (%)	67 (44.1)
Current smoker, n (%)	34 (22.4)
SBP, mm Hg	108.5 (9.9)
DBP, mm Hg	68.5 (8.5)
Mean arterial BP, mm Hg	81.9 (8.3)
Pulse pressure, mm Hg	40.0 (7.4)
Weight, kg	78.8 (18.0)
BMI, kg/m ²	27.0 (5.4)
Waist girth, cm	83.3 (14.0)
Total cholesterol, mmol/L	4.7 (1.0)
LDL cholesterol, mmol/L	2.7 (0.8)
HDL cholesterol, mmol/L	1.4 (0.4)
Triglycerides, mmol/L	1.2 (0.8)
Glucose, mmol/L	4.4 (0.4)
aPWV, cm/s	477.5 (97.4)
Annual change	
SBP change, mm Hg/y	-0.1 (4.6)
DBP change, mm Hg/y	2.2 (4.1)
Mean arterial BP change, mm Hg/y	1.4 (3.8)
Pulse pressure change, mm Hg/y	-2.3 (4.1)
Weight change, kg/y	1.2 (3.1)
BMI change, kg/m ² per year	0.4 (1.1)
Waist girth change, cm/y	2.2 (3.6)
aPWV change, cm/s per year	2.1 (46.8)

BMI indicates body mass index; BP, blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; aPWV, aortic pulse-wave velocity; SBP, systolic blood pressure; SD, standard deviation.

statistical significance ($P=0.030$). In all 3 multivariable models, baseline aPWV was significantly negatively associated with annual change in aPWV ($P<0.001$), whereas age, sex, baseline MAP, and MAP change were not significantly associated with annual change in aPWV. In model 3, blacks had an ≈ 15 cm/s per year larger annual increase in aPWV than whites ($\beta=15.5$, $P=0.024$). Interactions between obesity measures and age, sex, and race-ethnicity were tested in multivariable modeling and none was significant. However, although the race-ethnicity interaction was not significant, stratification of model 3 by race-ethnicity suggested that for a 2.3-kg (5-lb) weight gain, the effect on aPWV progression was greater for blacks ($\beta=6.1$ cm/s per year) than for whites ($\beta=3.7$ cm/s per year).

To examine whether the effects of weight change on aPWV change could be seen even with only minor changes in weight, multivariable adjusted weight change analyses were re-run excluding those with >4.5 kg (10 lb) annual weight gain or loss ($n=21$). The size of the effect remained nearly

TABLE 2. Effect of Baseline Covariates and Annual Change in Covariates on Annual Change in aPWV (cm/s per year) Adjusted for Baseline aPWV

Variable, Increment	β	95% CI	P
Baseline			
Age, 5 y	2.6	-2.8, 7.8	0.340
Female	10.0	-2.9, 22.9	0.126
Black race-ethnicity	21.8	9.1, 34.5	<0.001
SBP, 5 mm Hg	-0.25	-3.5, 3.1	0.902
DBP, 5 mm Hg	1.6	-2.3, 5.5	0.413
Mean arterial BP, 5 mm Hg	0.2	-0.6, 1.0	0.609
Pulse pressure, 5 mm Hg	-2.4	-6.7, 2.0	0.281
Current smoker	-9.1	-24.5, 6.3	0.244
Weight, 2.3 kg (5 lb)	1.0	0.1, 1.9	0.023
BMI, kg/m ²	2.6	1.4, 3.8	<0.001
Waist girth, cm	0.7	0.3, 1.2	0.003
Total cholesterol, 0.26 mmol/L (10 mg/dL)	1.1	-0.6, 2.9	0.210
LDL cholesterol, 0.26 mmol/L (10 mg/dL)	0.9	-1.1, 2.9	0.382
HDL cholesterol, 0.13 mmol/L (5 mg/dL)	1.7	-0.6, 4.0	0.153
Triglycerides, 0.11 mmol/L (10 mg/dL)	-0.02	-1.0, 0.9	0.969
Glucose, 0.56 mmol/L (10 mg/dL)	-2.8	-13.0, 7.4	0.591
Annual change			
SBP change, 5 mm Hg/y	3.4	-3.4, 10.3	0.325
DBP change, 5 mm Hg/y	-4.4	-12.2, 3.4	0.267
Mean arterial BP change, 5 mm Hg/y	-0.3	-2.0, 1.3	0.693
Pulse pressure change, 5 mm Hg/y	8.7	1.0, 16.3	0.026
Weight change, 2.3 kg/y (5 lb/y)	5.8	1.0, 10.5	0.019
BMI change, kg/m ² per year	5.2	-0.6, 11.0	0.080
Waist girth change, cm/y	0.1	-1.7, 2.0	0.907

CI indicates confidence interval.

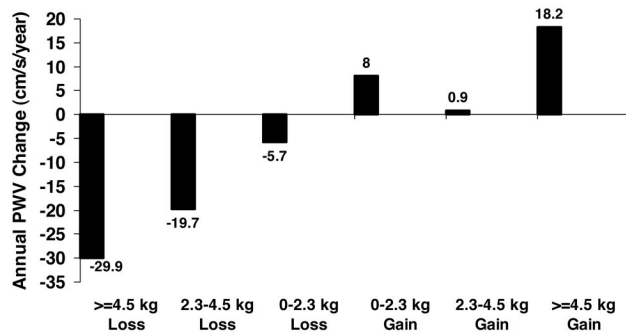
identical, estimated to be 6.1 cm/s per year per 2.3-kg (5-lb) annual increase in weight. However, because of the smaller sample size, this effect did not achieve statistical significance.

Weight change was categorized into 2.3-kg (5-lb) increments to graphically illustrate the strong association between weight change and aPWV change. Those experiencing weight loss had decreases in aPWV, whereas those experiencing weight gain had increases in aPWV (Figure).

TABLE 3. Multivariable-Adjusted* Models for Effects of Obesity Measures on Annual aPWV Change (cm/s per year)

Variable, Increment	β	95% CI	P
Model 1			
Baseline waist girth, cm	0.7	0.2, 1.2	0.009
Waist girth change, cm/y	0.7	-0.9, 2.4	0.387
Model 2			
Baseline BMI, kg/m ²	2.0	0.8, 3.1	0.001
BMI change, kg/m ² per year	5.3	0.3, 10.2	0.037
Model 3			
Baseline weight, 2.3 kg (5 lb)	0.8	-0.1, 1.7	0.087
Weight change, 2.3 kg/y (5 lb/y)	5.6	1.0, 10.2	0.017

*All models adjusted for baseline aPWV, time between visits, race-ethnicity, sex, age, baseline MAP, and change in MAP.



Annual aPWV change by weight change, adjusted for baseline aPWV, age, race-ethnicity, sex, baseline MAP, MAP change, and baseline weight.

To make certain that blood pressure changes resulting from weight changes were not driving associations, multivariable modeling was re-run twice, once replacing MAP with adjustment for baseline systolic blood pressure and change in systolic blood pressure, and the second time replacing MAP with adjustment for baseline pulse pressure and change in pulse pressure. Weight change showed very similar β values and remained significantly positively associated with change in aPWV in both models. Of interest, neither systolic blood pressure nor pulse pressure nor changes in these factors were significantly associated with change in aPWV in these multivariable models. Additionally, blood pressure changes were only borderline statistically significantly associated with weight changes. Annual systolic blood pressure change among weight change categories (≥ 4.5 kg loss, 2.3 to 4.5 kg loss, 0 to 2.3 kg loss, 0 to 2.3 kg gain, 2.3 to 4.5 kg gain, ≥ 4.5 kg gain) were -0.9 mm Hg/year, -2.5 mm Hg/year, 1.0 mm Hg/year, -0.9 mm Hg/year, 0.04 mm Hg/year, and 2.1 mm Hg/year, respectively ($P=0.053$).

Six individuals began use of antihypertensive, lipid-lowering, or thyroid medications between the baseline and follow-up visits. Results were unchanged when analyses were re-run excluding these 6 individuals.

Discussion

These data show that in these healthy young adults, both body mass index change and weight change are associated with change in aPWV. These associations were linear, such that annual weight gain was associated with an annual increase in aPWV, and annual weight loss was associated with an annual decrease in aPWV. These effects were present despite adjustment for aging, blood pressure changes, race-ethnicity, and gender. Additionally, exclusion of individuals who gained or lost >4.5 kg (10 lb) per year did not alter the magnitude of the association between weight change and aPWV change, suggesting that the association is constant across relatively minor changes in weight.

The annualized progression rates shown here are similar to those of the normotensive subjects younger than 50 years of age presented by Benetos et al in the only other nonpharmacological, longitudinal study of arterial stiffness published to date, according to the authors' knowledge.¹⁶ In that study of 6-year progression of arterial stiffness, baseline body mass index was not associated with progression of aPWV.¹⁶

However, the effects of body mass index were analyzed among a wider age range (including a large proportion aged older than 50 years), perhaps suggesting that the effects of body mass index may be limited to younger individuals such as those in the current study. Importantly, the current study extends the aPWV progression data presented by Benetos et al to blacks, showing that blacks had annual increases in aPWV ≈ 22 cm/s per year larger than whites before multivariable adjustment, and ≈ 15 cm/s per year larger after multivariable adjustment. This enhanced progression of arterial stiffening will be further accelerated by the effects of obesity, because black women are disproportionately represented in the obesity epidemic.¹ Although inconclusive, stratification of the weight change results in the current study suggested that for a given amount of weight gain, the effect on vascular stiffening was larger for blacks than for whites. These results will need to be replicated in a bigger population with enhanced power for stratified analyses. Enhanced arterial stiffness will likely contribute to a dramatic increase in clinical cardiovascular events among blacks.

In associations with aPWV change among these data, baseline obesity measures were independent of changes in obesity measures and vice versa. The independent effect of baseline weight/body mass index most likely represents the cumulative chronic effects of excess weight over time, whereas the independent effect of change in weight/body mass index suggests a more acute effect of weight on the vasculature. Acute effects suggest a reversible component to the effects of excess weight, supported by the regression of aPWV with weight loss in the current study. These data underscore the possible vascular benefits resulting from weight loss programs. Clinical trials examining the effect of weight loss on changes in aPWV are needed.

Additionally, the independence of the effects of weight gain from those of baseline weight suggests that weight gain affects the vasculature irrespective of one's starting weight. Therefore, even normal-weight individuals may have vascular consequences with moderate weight gain. This may have profound public health implications in an age of widespread weight cycling.

Weight gain may act through a number of possible mechanisms to elicit acute and chronic effects on the vasculature. Insulin is a powerful vasodilator,^{19,20} and the insulin-resistant state that commonly accompanies obesity²¹ impairs the vasodilatory effect of insulin, linking the insulin resistant state and obesity with vascular endothelial dysfunction.²² The higher levels of circulating insulin in the insulin resistant state may also be associated with vascular effects, such as proliferation of smooth muscle cells²³ and increases in collagen production.²⁴ High levels of glucose, as found in the insulin resistant state, have been shown to stimulate collagen synthesis and cross-linking between protein fibers.²⁵

Factors other than insulin may also play a role. Obesity is associated with low-grade inflammation, which has been shown to be an initiating factor in the development of atherosclerosis.²⁶ Angiotensin II released from adipocytes, themselves, may be another mechanism behind obesity-associated vascular damage.²⁷ Higher levels of angiotensin II cause increased sodium retention, resulting in increases in

circulating blood volume and changes in shear stress, both of which can elicit vascular changes.²⁸ Inhibition of angiotensin-converting enzyme has been shown to reduce arterial stiffness,²⁹ as has a low-salt diet.³⁰ Additionally, we have previously shown in this same population a strong relationship between obesity and larger arterial diameters and wall thickening.³¹ Dilation and wall thickening may predispose the arteries of obese individuals to more rapid arterial stiffening.

It is yet unclear which of these mechanisms elicits reversible versus irreversible vascular damage. It may be that restoration of the nitric oxide system, the system that underlies endothelial-dependent vasodilation,³² could restore endothelial function, returning arterial stiffness levels to baseline or "normal." However, certain changes in collagen and protein cross-linking may be irreversible, eliciting permanent increases in arterial stiffness. Further determination of the reversibility of mechanisms underlying obesity-associated vascular damage could have implications for the treatment of obesity-related vascular damage, and the cardiovascular prognosis of obese individuals. Additionally, the majority of the literature has examined these associations in obese individuals. Given our results, which suggest that weight gain may result in vascular changes even in nonobese individuals, future research examining the pathophysiological effects of weight changes in nonobese individuals is warranted.

Some data have suggested that central obesity, specifically, is responsible for obesity-associated vascular changes.^{33,34} In our study, aPWV change was associated with baseline waist circumference, a crude measure of central adiposity, but not with change in waist circumference. Measurement variability in waist circumference may have limited our ability to detect an effect of change in waist circumference on aPWV change. Both a larger sample size and a more precise measure of central obesity are needed to adequately explore this question.

It is of note that blood pressure values were not strongly associated with aPWV change in this sample and that associations between arterial stiffness progression and both weight and body mass index increases were independent of blood pressure. Additionally, the effect of weight change on aPWV change was much stronger than the effect of weight change on blood pressure change. These observations strongly suggest that the relationships shown here between arterial stiffness changes and changes in weight and body mass index were not driven by weight-associated changes in blood pressure.

Despite the linearity of the association between weight change and aPWV change, and its consistency with previous cross-sectional findings in this population,¹⁵ the results of the current study should be interpreted with caution. Replication of these findings in a larger sample with a longer duration of follow-up is warranted.

Perspectives

These data show strong associations between weight gain and progression of arterial stiffness. Perhaps more importantly, these data also show regression of arterial stiffness with weight loss. The associations between weight change and progression/regression of arterial stiffness were seen even among nonobese individuals. These data also showed greater

vascular stiffness progression among blacks compared with whites, which portend substantial adverse cardiovascular consequences for blacks given the disproportionate numbers of black women, especially, with obesity.¹ Given the young age of the individuals in this study, these data greatly underscore the vascular benefit of weight loss among overweight and obese individuals and the need for successful weight loss and weight gain prevention programs among young adults. Targeted weight loss programs for blacks should be considered.

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