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Cardiovascular risk factors associated with enlarged diameter of the abdominal aortic and iliac arteries in healthy women

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Abstract

The abdominal aorta is known to be more susceptible to arterial dilation than to occlusion primarily due to the effects of vascular aging. Few studies have considered the effects of cardiovascular risk factors on arterial diameter, particularly within a population of healthy women at mid-life. This study seeks to examine associations between cardiovascular risk factors and abdominal aortic and iliac adventitial diameter.

Abdominal aortic ultrasound was performed in 260 post-menopausal women aged 53.9 ± 2.5 years at time of scan as a component of the Healthy Women Study. Risk factors were evaluated at premenopause and post-menopausal clinic visits closest in date to the abdominal ultrasound scan. Post-menopausal weight and change of weight from pre- to post-menopause were among the strongest correlates of larger adventitial diameter after controlling for age, systolic blood pressure, and body size using height. Other post-menopausal risk factors significantly correlated with both abdominal aortic and iliac diameter were BMI, waist circumference, HDL, and insulin ($p < 0.05$).

These data suggest that weight is a key risk factor in the promotion of vascular aging as indexed by enlarged arterial diameter. Women at mid-life should continue to be targeted for weight interventions to reduce their risk for more serious cardiovascular complications.

Keywords: Vascular aging; Diameter; Weight; Abdominal aorta

1. Introduction

Vascular aging, while occurring concomitantly with atherosclerosis is infrequently distinguished from subclinical disease processes. With increasing age, arteries change in their structural and functional capacities. These changes are diffuse throughout the arterial tree and affect the endothelium, arterial intima and media. Age-associated increases in intima–media thickening are attributable to degeneration of elastin fiber and increases in collagen within the media [1]. Simultaneous with this thickening are increases in luminal dilatation and stiffness as well as endothelial dysfunction [2]. Arterial diameter can be used as a marker of this overall aging process.

Vessels within the aortic region are especially known to be more susceptible to arterial dilation than to occlusion primarily due to the effects of vascular aging [3]. Several risk factors, such as elevated blood pressure and atherosclerosis, may accelerate these age-related changes and as a result contribute to adverse clinical outcomes such as aortic aneurysms and coronary heart disease [3–8]. It is therefore of public health significance to identify those risk factors which contribute to vascular aging as measured by arterial diameter.

The effects of risk factors on arterial diameter, have been characterized in the carotid [9,10], coronary [11,12], and brachial vessels [13], but have not been extensively studied in the abdominal region. Although several studies have ex-

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amined cardiovascular risk factors and their relationship to abdominal aortic aneurysms, few have looked at these factors in terms of vascular aging. It is important to independently characterize the associations between potential cardiovascular risk factors and their impact on the vascular aging of vessels since risk factors may impact various vascular regions differently. Once these associations are better characterized, the aging of vessels may be addressed from a more clinical perspective.

Cardiovascular risk factors may also help explain observed gender differences regarding arterial dilation and vascular aging. Males have been found to have a larger aortic diameter relative to their body size and stiffer abdominal aortas compared to women and thus have been studied to a greater extent [4,14–18]. To our knowledge, potential differences between the association of pre- and post-menopausal risk factors with aortic diameter has not been examined in any population. The purpose of this study is therefore to investigate whether traditional cardiovascular risk factors, measured pre- and post-menopause, and atherosclerotic measures are associated with abdominal aortic diameter among a population of healthy women and if so, which are the strongest predictors of larger adventitial diameter.

2. Methods

2.1. Study population

The Healthy Women Study (HWS) is a longitudinal cohort study designed to evaluate the changes in coronary risk factors that are attributable to natural menopause. Five hundred and forty-one healthy, initially pre-menopausal women, aged 42–50 years of age, living in Pittsburgh, PA were recruited in 1983 and 1984. As previously described [19], eligibility criteria included diastolic blood pressures of less than 100 mmHg, no hormone replacement therapy use, no medication use for chronic disease including hypertension, and having a menstrual cycle within 3 months of the baseline examination. Women were followed through their menopausal transition. A woman was defined as being post-menopausal once she ceased cycling and/or used HRT in combination for 12 consecutive months. Follow-up evaluations were subsequently conducted at 1, 2, 5, and 8 years post-menopause.

2.2. Abdominal aortic ultrasound evaluation

As an adjunct component to the Healthy Women Study, ultrasound measures of subclinical atherosclerosis in the abdominal aorta were performed in 260 HWS participants. Abdominal aortic ultrasound was performed in conjunction with the participants' second carotid ultrasound evaluation in the HWS. Aortic ultrasound testing was conducted at the University of Pittsburgh Department of Epidemiology, Ultrasound Research Laboratory (Pittsburgh, PA), using a Toshiba SSA 270A duplex scanner with a 3.75 MHz convex probe. The protocol was based on that used in the Cardiovascular Health Study (CHS) with the addition of iliac artery imaging [20]. The reproducibility of this protocol was also validated by Alcorn et al. [20] and resulted in Pearson and intraclass correlation coefficients of greater than or equal to 0.87 for the suprarenal and infrarenal diameter measurements and the infrarenal to suprarenal diameter ratio.

Briefly, trained registered vascular technologists obtained B-mode gray scale images of the abdominal aorta in the transverse projection. Scans were recorded on Super VHS tape and subsequently scored by certified readers. Aortic diameter was measured at suprarenal, infrarenal, 2 cm proximal to the iliac bifurcation, and at the first centimeter of the right and left iliacs from outer wall to outer wall. More specifically, suprarenal images were taken 1 cm distal to the origin of the superior mesenteric artery, just above the level of the left renal artery, with either artery being visualized in order to accept the image for measurement. The infrarenal measurement was taken below the renal arteries at the site of maximum aortic artery diameter (adventitia plus wall). Intima–media thickness (IMT) measurements were also made at each of the above locations using the far wall interface. The above protocol was employed to screen for aneurysms defined as an infrarenal aortic diameter greater or equal to 3.0 cm or an infrarenal to suprarenal diameter ratio greater or equal to 1.2.

Adventitial diameter and intima–media thickness measurements at each of the five locations evaluated were averaged to obtain a combined aorta/iliac value. Measurements from the suprarenal aorta, infrarenal aorta, and 2 cm proximal to the iliac bifurcation were averaged to create a mean abdominal aortic value for adventitial diameter and IMT. Lastly, measurements from the first centimeter of the right and left iliacs were averaged to create a mean iliac value for adventitial diameter and IMT. These mean values were subsequently used for analysis.

2.3. Clinic visits

Previous HWS publications have described in detail the components and methodology used in the baseline (pre-menopausal) and post-menopausal clinic examinations [19,21]. The baseline clinic examination consisted of blood pressure, height, weight, waist circumference, and a 12-h fasting blood sample for glucose, insulin, apoprotein, and lipoprotein measurements. A 75-g glucose load was administered immediately preceding blood sampling. Blood samples were assayed at the lipid laboratory of the University of Pittsburgh Graduate School of Public Health, a Centers for Disease Control and National Heart Lung and Blood Institute certified laboratory. Levels of total serum cholesterol, total HDL cholesterol, and triglycerides were determined using standard assays [22–24]. LDL cholesterol was estimated from the Friedewald equation [25]. Plasma glucose was determined by enzymatic assay and plasma insulin by radioimmunoassay.

These measures were repeated at each of the post-menopausal (post) clinic visits, first, second, fifth, and eighth post. Insulin measures were not available for all participants. Women were also asked whether or not they were taking hormone replacement therapy and if so, what regimen they were currently using. Post-menopausal risk factors were ascertained from data at the post-menopausal clinic visit closest in date to the abdominal aorta scan. Fifty percent of the women were 8 years post-menopause at the time of their abdominal aorta scan, 48.5% were 5 years post-menopause, 1% were 2 years post-menopause, and 0.5% were 1 year post-menopause. The mean difference between the date at which risk factors were evaluated and the date of the abdominal ultrasound scan was 2 months.

2.4. Statistical methods

Of the 260 participants who had an abdominal aortic ultrasound, 41 women had missing data with respect to both their right and left iliac diameters ($N = 38$) or their left iliac diameter alone ($N = 2$). One participant had missing data for measurements made at the proximal location. All data were analyzed by SAS Statistical Software v8.2 (Cary, NC). Statistical significance was defined as a p-value <0.05.

Differences between baseline and post-menopausal risk factors were assessed with paired t-test or with the Wilcoxon-rank sum test for non-normally distributed data. A chi-square statistic was used to assess the differences in current smoking status between the baseline and post-menopausal visit. Change scores were calculated by subtracting baseline clinic values from post-menopausal clinic values.

The univariate associations between risk factor levels and abdominal aortic/iliac adventitial diameter and IMT were evaluated with Pearson correlation coefficients, with the exception of triglycerides, insulin, smoking, and hormone use, whose associations were measured using a Spearman correlation coefficient. Partial correlations were calculated to adjust for body size (height), age and systolic blood pressure. Adjustment for systolic blood pressure and height was required due to the strength of their individual correlation with abdominal aortic diameter. Height, as opposed to body-mass index, was chosen as a measure of body size so that weight could be evaluated as an independent risk factor. Adjustment for age was undertaken because of its known relationship with vascular aging as evidenced in cardiovascular literature.

The relationship between change in risk factors and vessel diameters was also evaluated using multivariable stepwise linear regression analysis. Baseline age, systolic blood pressure, and height were forced into the models followed by those baseline risk factors and their corresponding change scores from pre-to post-menopause which were significant at the $p < 0.05$ level.

3. Results

Risk factor data for the baseline and the post-menopausal clinic visit closest in date to the abdominal scan are presented in Table 1. Significant differences ($p < 0.001$) between values measured pre- versus post-menopause were noted for all variables with the exception of diastolic blood pressure and HDL. Of particular interest was the 10 mm increase in pulse pressure, the blood pressure parameter most closely tied to arterial stiffness. Additionally, while both weight and girth measurements increased between baseline (pre-menopausal) and post-menopausal exams, average height decreased.

At the time of abdominal aortic ultrasound, the mean age of participants was 53.9 ± 2.5 years. The mean aortic and iliac adventitial diameters were 17.9 ± 1.54 and 11.23 ± 1.33 mm, respectively. Fig. 1 presents the distribution of the adventitial

Table 1
Population description—baseline and post-menopausal clinic visits ($N = 260$)

	Baseline	5–8 years post-menopauset[a]	p-value
Age (years)	47.7 ± 1.5	53.9 ± 2.5	<0.001
Systolic blood pressure (mmHg)	108.0 ± 11.0	118.4 ± 16.6	0.025
Diastolic blood pressure (mmHg)	72.0 ± 7.7	72.0 ± 9.6	0.999
Pulse pressure (mmHg)	36.0 ± 7.4	46.4 ± 10.9	<0.001
Body-mass index (kg/M^2)	24.4 (17.4, 40.9)	26.9 (16.9, 48.7)	<0.001
Weight (kg)	65.3 ± 12.1	70.8 ± 14.8	<0.001
Waist circumference	79.0 ± 11.5[b]	81.9 ± 13.0	<0.001
Hip circumference	102.5 ± 11.1[b]	104.9 ± 12.0	<0.001
Height (cm)	162.0 ± 6.3	162.0 ± 6.3	<0.001
Cholesterol (mg/dL)	184.7 ± 30.9	212.3 ± 35.4	<0.001
HDL (mg/dL)	60.8 ± 14.1	61.0 ± 15.8	0.845
LDL (mg/dL)	107.8 ± 29.0	127.8 ± 34.3	<0.001
Triglycerides (mg/dL)	66.0 (33.0, 314.0)	99.5 (37.0, 396.0)	<0.001
Glucose (mg/dL)	86.3 ± 9.5	90.0 ± 14.8	<0.001
Insulin	6.4 (3.0, 51.9)	13.5 (5.3, 63.9)[c]	<0.001
% Smoking	30.1	13.3	<0.001
% HRT use	–	50.7	–

[a] Two participants were 2 years post-menopause and one participant was 1 year post-menopause.
[b] $N = 59$.
[c] $N = 136$.

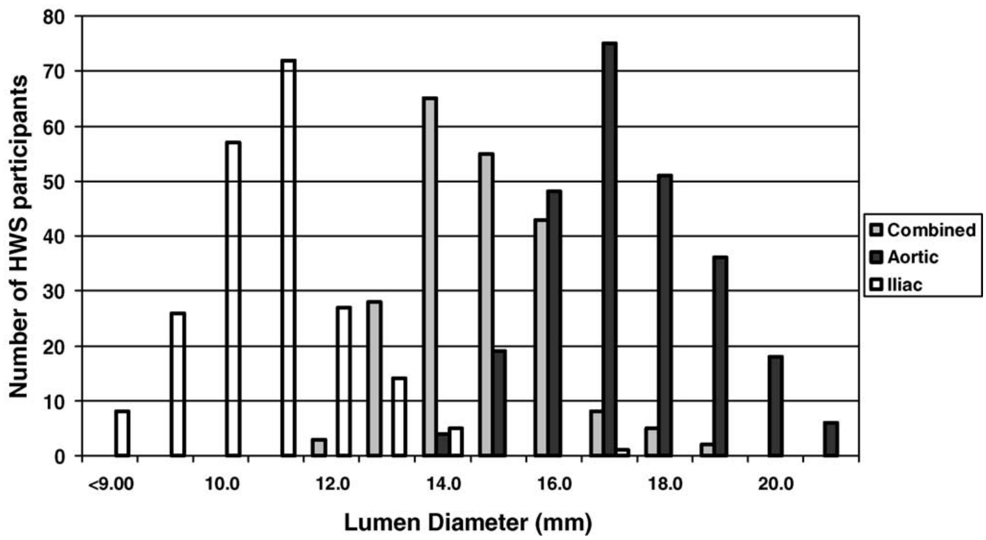

Fig. 1. Distribution of abdominal aorta adventitial diameters within the Healthy Women Study.

diameters and includes the "combined" diameter, an average of all aortic and iliac measurements. None of the women met the criteria for an abdominal aortic aneurysm. The mean aortic IMT was 2.04 ± 0.43 mm with a range of 1.05–3.74 mm. The mean iliac IMT was 1.60 ± 0.41 mm with a range of 0.79–3.23. IMT was highly correlated with adventitial diameter ($r = 0.330$, $p < 0.0001$ for aortic segment and $r = 0.353$, $p < 0.0001$ for iliac segment). After adjustment for age, systolic blood pressure, body size using height, triglycerides, HDL, and other risk factors related to both diameter and IMT, these associations were equivalent or even stronger.

Table 2 presents the results of the correlations between post-menopausal risk factors and aortic and iliac adventitial diameter. For both of these locations weight, waist circumference, HDL, and insulin were significantly associated with adventitial diameter independent of age, SBP, and height. Correlations between abdominal aortic diameter and change in risk factors from baseline to post-menopausal clinic visit closest in date to the abdominal aortic ultrasound were also calculated. These correlations were adjusted for baseline (pre-menopause) measures. Change in age was not adjusted for given that duration within the periomenopasue period only varied between 5 and 8 years for more than 99% of women and upon preliminary analysis had little effect on the correlation coefficients. An increase in weight ($r = 0.155$ and 0.307), BMI ($r = 0.164$ and 0.252), insulin ($r = 0.214$ and 0.292), and

Table 2
Correlations between risk factors measured 5–8 years post-menopause and abdominal aortic and iliac adventitial diameter

Post-menopause risk factors	Abdominal aortic adventitial diameter				Iliac adventitial diameter			
	Unadjusted ($N = 258$)		Adjusted ($N = 253$)		Unadjusted ($N = 210$)		Adjusted ($N = 205$)	
	r	p-value	r	p-value	r	p-value	r	p-value
Age	0.075	230			0.044	0.525		
SBP	0.238	<0.001			0.110	0.113		
DBP	0.270	<0.001			0.189	0.006		
Pulse pressure	0.125	0.246			0.0003	0.996		
Height	0.246	<0.001			0.227	<0.001		
BMI[a]	0.380	<0.001			0.406	<0.001		
Weight	0.418	<0.001	0.347	<0.001	0.486	<0.001	0.433	<0.001
Waist circumference	0.369	<0.001	0.325	<0.001	0.403	<0.001	0.376	<0.001
Cholesterol	0.061	0.330	0.084	0.183	0.034	0.627	0.059	0.408
LDL	0.100	0.111	0.133	0.036	0.094	0.178	0.125	0.077
HDL	−0.220	<0.001	−0.234	<0.001	−0.187	0.007	−0.212	0.003
Triglycerides	0.141	0.025	0.137	0.031	0.048	0.491	0.047	0.512
Glucose	0.188	0.003	0.165	0.009	−0.015	0.828	−0.042	0.556
Insulin[a,b]	0.223	0.009	0.219	0.012	0.295	0.001	0.396	0.001
Smoking[a]	0.064	0.380	0.018	0.805	0.060	0.460	0.026	0.746
Hormone use[a]	−0.095	0.128	−0.127	0.046	−0.023	0.741	−0.034	0.634

Adjusted controlled for age, systolic blood pressure, and height.
[a] Spearman correlations.
[b] $N = 135$ for aorta and 114 for iliac diameter.

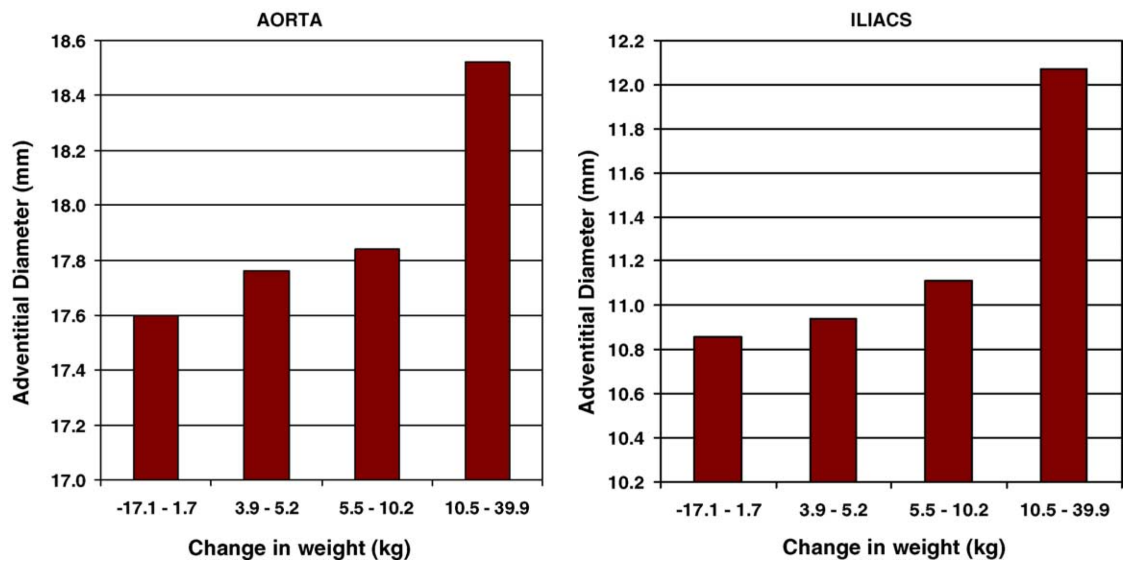

Fig. 2. Age, systolic blood pressure, and height adjusted mean diameter by quartiles of weight change.

a decrease in HDL ($r = -0.210$ and -0.189) were significantly correlated ($p < 0.01$) with a greater adventitial diameter in the aortic and iliac segments, respectively. A positive correlation between change in LDL and iliac adventitial diameter was also noted ($r = 0.139$, $p = 0.048$). Change in glucose was positively correlated with aortic adventitial diameter as well ($r = 0.171$, $p = 0.007$). Fig. 2 shows the relationship between quartiles of weight change and aortic and iliac diameter.

The results of stepwise multivariable regression found that change in weight independent of age, height, systolic blood pressure, and baseline weight, was the strongest predictor of greater adventitial diameter ($\beta_{aorta} = 0.043$ and $\beta_{iliac} = 0.064$, $p = <0.01$). After controlling for pre-menopause weight and change in weight, little else added further predictive value.

A total of 101 women reported HRT use at their post-menopausal exam. HRT users had lower LDL cholesterol ($p = 0.026$), higher HDL cholesterol ($p = 0.0003$), and higher triglycerides ($p = 0.033$), but did not differ with respect to any other post-menopausal clinic risk factors. Unadjusted and age, SBP, and height adjusted mean adventitial diameter were not significantly different among hormone and non-hormone users.

Lastly, the association between risk factors and abdominal aortic intima–media thickness were evaluated in this population. LDL and insulin correlated positively and significantly with IMT in the iliac arteries. No post-menopausal risk factors correlated significantly with either abdominal aortic or iliac IMT segments before and after adjustment for age, SBP, and height.

4. Discussion

This study examined the correlation between cardiovascular risk factors and abdominal aortic diameter within a population of healthy post-menopausal women. The primary finding of the present study was that weight independent of age, blood pressure, and height, is a key risk factor in vascular aging as evidenced by increased aortic diameter. These data extend previous research by demonstrating that change in weight from pre- to post-menopause contributes to greater abdominal arterial dilation.

Our results are in agreement with a study by Paivansalo et al. [15] where body-mass index was significantly correlated with higher adventitial diameter, as measured by ultrasound, in both women and men aged 40–60 years. Aortic diameters were nearly equivalent between the two female populations, 17.2 ± 1.4 mm in Paivansalo et al. and 17.9 ± 1.5 mm in the present report. Correlations between BMI ($r = 0.172$, $p = <0.001$) and height ($r = 0.236$, $p = <0.001$) and aortic adventitial diameter were consistent with our analysis. Surprisingly, systolic blood pressure was not independently correlated with aortic diameter ($r = 0.060$) in the Paivansalo population. Diastolic blood pressure was however, strongly correlated with both aortic and iliac arterial diameter ($p < 0.001$). HDL ($r = -0.141$, $p = 0.002$) and triglycerides ($r = 0.092$, $p = 0.043$) were also correlated with iliac diameter. Glucose was not significantly related with increased aortic or iliac diameter in their population and insulin data were not reported.

In our analysis, a strong positive association between vessel diameter and intima–media thickness was also observed. Paivansalo et al. found a significant association between aortic dilation and another atherosclerotic measure, aortic plaques. The progressive increase in vessel diameter has been hypothesized as a compensatory mechanism to atherosclerosis. Atherosclerosis can promote vascular aging by increasing arterial stiffening and in its more severe forms cause medial degeneration and subsequent aneurismal development [1].

In the present study, change in weight, BMI, insulin, and HDL through menopause was associated with larger aortic diameter as well. It can be hypothesized that the increased insulin levels which accompany weight gain are related to a subsequent increase in aortic diameter. This is supported by multivariable results where change in weight entered the model in addition to premenopause weight, age, height, and systolic blood pressure. Additionally, after adjusting for weight in partial correlations, the association between insulin, glucose, and triglycerides with adventitial diameter was no longer significant.

The effects of cardiovascular risk factors, particularly weight, on arterial dilation have previously been observed in the carotid vascular bed as well [9,10,26,27]. Collectively, these findings suggest that weight is a risk factor which should be addressed early to slow the progression of vascular aging. This may be especially true in women who experience a significant weight gain with age [28,29] and the menopausal transition [30,31]. The observed positive correlations between change in weight and BMI support this statement.

There are several mechanisms whereby weight can impact arterial dilation. Insulin may act as a vasodilator via endothelium-derived nitric oxide release [32]. Correspondingly, insulin resistance along with higher leptin levels and releases of angiotensin II accompanying obesity may promote sympathetic outflow [33–35]. This sympathetic outflow is received by the kidneys causing sodium retention and subsequent increased circulating fluid volume. Prompted by an increase in shear stress, the arteries then dilate to accommodate the increased fluid volume [36].

The susceptibility to dilation of the abdominal aorta is in part, related to the collagen/elastin makeup of the aortic wall. While central arteries have a higher concentration of elastin than peripheral arteries [37], age-associated changes in the collagen to elastin ratio occur at a greater rate in central compared to peripheral arteries [38]. It has particularly been noted in the abdominal aorta that the ratio of collagen to elastin differs within its various regions making the vessel as a whole more prone to wall instability and corresponding dilatation [1,37,39]. As a result of the decrease in elastic wall elements, stress is also transferred to the collageneous elements in the arterial wall [40,41]. Thus, at the same time the arteries dilate, they also become stiffer, another hallmark of vascular aging.

Vascular aging as evidenced by arterial stiffening has been linked with an increased risk of clinical cardiovascular events such as stroke, coronary heart disease, and death [42,43]. Our data demonstrate that weight and weight gain at mid-life are associated with vascular aging as evidenced by arterial dilation. This suggests that women at mid-life should be targeted for the prevention of weight gain. It is possible that the arterial changes accompanying weight gain may explain some of the change in cardiovascular risk at mid-life.

Finally, our observation that few risk factors (LDL and insulin) were associated with abdominal aortic IMT was not surprising. As arteries dilate, the intima and media thin and thus the true relationship between CVD risk factors and aortic IMT may be masked. The measurement of IMT in the aorta is also difficult, due to its depth, and thus reflected signals may provide less information than in more surface vessels.

While the results of this study may aid in future prevention efforts against cardiovascular disease in healthy women, there remains a need to confirm these results in larger and more diverse populations in a prospective manner. Further research should also consider the changes in more sophisticated measures of body composition in conjunction with abdominal aortic diameter. Despite these limitations, it is apparent that blood pressure and weight are significant risk factors in increasing arterial diameter and subsequent aging of vessels, further supporting the necessity to control these factors early on.

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