Original Article

Overweight Body Mass Index Classification Modifies Arterial Stiffening Associated with Weight Gain in Healthy Middle-Aged Japanese Men

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The present study was conducted to clarify whether body mass index (BMI [kg/m^2]) classifications (*i.e.*, without excess weight, overweight, and obese) modify the rate of progression of arterial stiffening, a cardiovascular risk factor associated with weight gain. A 3-year observational study was conducted in 2,080 healthy middle-aged Japanese men (aged 42±10 years). Brachial-ankle pulse wave velocity (baPWV) was measured at the beginning and end of the study period. In overweight subjects (30>BMI≥25), the estimated annual rate of increase of baPWV (ARbaPWV) in subjects with weight gain (≥5% weight gain; ARbaPWV, 21.8±4.4 cm/s/year) was significantly higher than in those without weight gain (<5% weight gain; ARbaPWV, 12.5±1.6 cm/s/year), after adjustments for changes in blood pressure and other variables ($p<0.05$). This change was not observed in subjects without excess weight (BMI<25) or in obese subjects (BMI≥30). The increase in the ARbaPWV associated with weight gain in the overweight group was also higher than that in the without excess body weight or obese groups. Our study revealed that the BMI classifications modified the annual rate of increase in arterial stiffening associated with weight gain. Weight gain seemed to accelerate arterial stiffening in overweight subjects, but not in subjects without excess weight. The weight gain in overweight subjects seemed to worsen the cardiovascular risk related to arterial stiffness in middle-aged healthy Japanese men. Thus, the prevention of weight gain should be emphasized in overweight subjects. (*Hypertens Res* 2008; 31: 1087–1092)

***Key Words*: arterial stiffness, weight gain, obesity, overweight**

Introduction

Excess weight (body mass index [BMI] ≥25 kg/m^2) and/or weight gain have been reported to increase the risk of atherosclerotic cardiovascular events (*1–3*). Increased arterial stiffness, as assessed using the pulse wave velocity (PWV), is a well-known cardiovascular risk factor (*4*) and is a predictor of future cardiovascular events (*5*). Some cross-sectional studies have demonstrated an increased arterial stiffness in subjects with excess weight (*6*, *7*), and a recent prospective study has demonstrated that weight gain was independently associated with an increase in arterial stiffness in young subjects (*8*). Several factors have been proposed to explain the correlation between increased arterial stiffness and excess weight and/or weight gain (*9*, *10*). However, whether weight gain increases arterial stiffness similarly in subjects with or without excess weight remains unclear. Furthermore, the BMI classifications for excess weight are overweight (25.0 kg/m^2 ≤BMI<30 kg/m^2) and obese (BMI ≥30 kg/m^2) (*2*), but the increases in arte-

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rial stiffness associated with weight gain in overweight and obese individuals have not been compared.

The present prospective study in healthy middle-aged Japanese men was conducted to clarify whether the BMI classifications (*i.e.*, without excess weight, overweight and obese) may modify the rate of progression of arterial stiffening associated with weight gain.

Methods

Design and Subjects

This follow-up study was performed in Japanese male employees of a single large construction company. From May 2000 to December 2004, the routine annual health checkup included an evaluation of atherosclerotic risk factors, and brachial-ankle PWV measurements were also conducted on two occasions: at the beginning (1st examination) and end (2nd examination) of a 3-year study period. The details of this follow-up study protocol are described elsewhere (*11*). At the baseline period of this follow-up study (from May 2000 to August 2001), a total of 3,396 subjects had an annual health checkup. Among them, 398 subjects who were working at branch offices and 609 female subjects were excluded because of the difficulty in entering them into the follow-up protocol (*e.g.*, They frequently change their job). Therefore, a total of 2,389 Japanese male subjects who were working at the company headquarters were enrolled in this follow-up study. At the 1st examination, 4 subjects who had an ankle/brachial systolic blood pressure index (ABI) of less than 0.95, 5 subjects who had atrial fibrillation, 4 subjects who were under maintenance hemodialysis, and 194 subjects who were receiving medication for hypertension, dyslipidemia, diabetes mellitus, heart disease or stroke were excluded from the analysis. During the study period (spanning the 1st and 2nd examinations), 3 subjects were newly diagnosed as having atrial fibrillation and 99 subjects began receiving medication for one or more of the above-mentioned diseases. Finally, data from 2,080 subjects were included in the present analysis (*10*).

Subjects with atherosclerotic risk factors were advised to visit the Health Care Center of their construction company as a first step, and a management plan was created for each subject. The subjects were provided guidance with regard to therapeutic lifestyle modifications. In subjects who were judged to require medication, the appropriate medication was prescribed. Subjects with an ABI of less than 0.95 or atrial fibrillation were considered ineligible for enrollment, because measurements of brachial-ankle PWV in persons with atrial fibrillation or an abnormal ABI are not considered accurate. In addition, subjects who were receiving medication for hypertension, dyslipidemia, diabetes mellitus, heart disease and/or stroke were also excluded from this study. Verbal informed consent was obtained from all of the participants prior to their participation. The protocol of this study conformed to the principles of the Declaration of Helsinki, and the study was conducted with the approval of the Ethical Guidelines Committee of Tokyo Medical University.

Pulse Wave Velocity Measurements

Brachial-ankle PWV was measured using a volume-plethysmographic apparatus (Form/ABI; Colin Co. Ltd., Komaki, Japan), in accordance with a previously described methodology (*11*, *12*). In brief, electrocardiographic electrodes were placed on both wrists, and a microphone for the phonocardiogram was attached to the left side of the chest. Electrocardiograms and phonocardiograms were used as timing markers for the device. Occlusion cuffs, which were connected to both plethysmographic and oscillometric sensors, were tied around both upper arms and ankles while the subjects lay in a supine position. The brachial and post-tibial arterial pressures were measured using the oscillometric sensor. The brachial and post-tibial arterial pressure waveforms were recorded for 10 s using a plethysmographic sensor and were stored. The waveform characteristics were determined automatically according to the phase-velocity theory. The measurements were conducted after the subject had rested for at least 5 min in a supine position in an air-conditioned room (24–26°C) earmarked exclusively for this purpose. The inter-observer and intra-observer coefficients of variation for PWV measurements have been reported to be 8.4% and 10.0%, respectively (*12*). The heart rate and mean arterial pressure simultaneously obtained during the measurement of the brachial-ankle PWV were used for the analyses; the blood pressure was recorded simultaneously from the right arm and the left arm using an oscillometric method, and the blood pressure variables were calculated as the means of the values measured for the right and left arms.

Laboratory Measurements

The serum levels of total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL) and creatinine, and the fasting plasma glucose (FPG) level were measured using enzymatic methods (Falco Biosystems Co. Ltd., Tokyo, Japan). All blood samples were obtained in the morning after the subjects had fasted overnight.

Statistical Analysis

All data were expressed as the mean±SD. Error bars are shown in all the figures. The significant differences between the variables at the 1st and 2nd examinations were assessed in each group using a paired *t*-test.

The percent change in the body weight was estimated as {(value at 2nd examination − value at 1st examination) × 100/value at 1st examination}. The estimated annual rate of increase in the brachial-ankle PWV value (ARbaPWV) was calculated using the formula (brachial-ankle PWV at 2nd

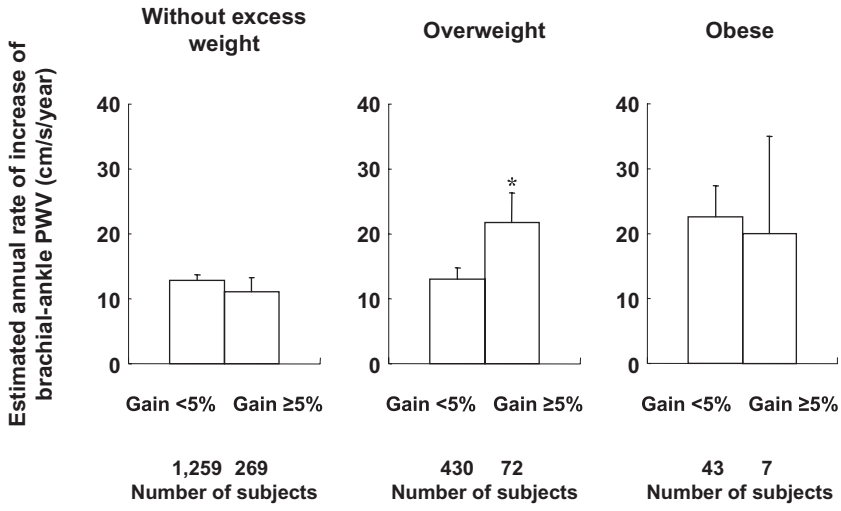

Fig. 1. *Adjusted values of estimated mean annual rate of increase in brachial-ankle pulse wave velocity between subjects with and those without weight gain in the without excess weight, overweight and obese groups. Gain ≥5%, subjects with weight gain; gain < 5%, subjects without weight gain. *p < 0.05 vs. subjects without weight gain.*

examination − brachial-ankle PWV at 1st examination)/3 (years). Differences in the ARbaPWV were compared among the groups using an analysis of covariance. This analysis was adjusted for continuous variables (values at first examination [age, BMI, brachial-ankle PWV, mean arterial pressure and heart rate recorded during the brachial-ankle PWV measurement, and TC, TG, HDL and FPG levels] and changes in the mean arterial pressure and heart rate recorded during the brachial-ankle PWV measurements, and the TC, TG, HDL and FPG levels measured during the study period) and categorical variables (smoking status at the first examination and changes in the smoking status during the study period). All analyses were conducted using SPSS software for Windows, version 11.0J (SPSS, Chicago, USA). p values <0.05 were considered significant.

Results

Significant weight gain was defined as a weight gain of more than 5% during the study period (*13*). In the entire study population ($n=2,080$), the adjusted value of ARbaPWV (12.2±1.7 cm/s/year) in the subjects with weight gain ($n=348$) was similar to that (13.9±0.7 cm/s/year) in the subjects without weight gain ($n=1,732$).

The BMI classifications were defined as follows: without excess weight, BMI < 25 kg/m^2; overweight, 30 > BMI ≥ 25 kg/m^2; and obese, BMI ≥ 30 kg/m^2. Figure 1 shows the ARbaPWV in subjects with or without weight gain according to the three BMI classifications. In the overweight group, the ARbaPWV in the subjects with weight gain was higher than that in the subjects without weight gain, even after adjustment. The ARbaPWV was similar between the subjects with and those without weight gain in the without excess weight group and in the obese group (Fig. 1). In addition, the difference in ARbaPWV was not significant between the subjects with ($n=79$) and those without weight gain ($n=473$) in an excess weight group (*i.e.*, the overweight plus obese groups) (adjusted ARbaPWV values: subjects with weight gain, 21.2±5.5 cm/s/year *vs*. subjects without weight gain, 14.0±4.7 cm/s/year; $p=0.1$).

The clinical characteristics of the three BMI classifications groups divided further into two groups with or without weight gain are shown in Table 1. In subjects with weight gain, the without excess weight and overweight groups showed significant increases in mean blood pressure, TC and TG levels during the study period, but a significant increase in the FPG level was not observed in these two groups (Table 1).

The increase in the ARbaPWV associated with weight gain in the overweight group, but not in the obese group, was higher than that in the without excess body weight group, after adjustment (Fig. 2).

Discussion

To our knowledge, the present study is the first report to demonstrate that BMI classifications (*i.e.*, without excess body weight, overweight, and obese) modify the annual progression of arterial stiffness associated with weight gain. To date, only one prospective study has demonstrated an association between weight gain and arterial stiffening in healthy young adults, and that study suggested that the effects of weight gain on arterial stiffening were independent of the baseline BMI (*8*). While aging and an increased BMI are determinants of arterial stiffness (*4*, *7*, *8*, *14*), the subjects of the previous study were relatively young and more than 75% of them were categorized as overweight or obese (the mean BMI in the

Table 1. Changes in Clinical Characteristics Associated with Weight Gain in Subjects Divided According to Body Mass Index Classifications

Without excess body weight ($n=1,528$)

	Weight change			
	Gain <5% ($n=1,259$)		Gain ≥5% ($n=269$)	
	Baseline	Year 3	Baseline	Year 3
Age	41±9		39±9	
Weight (kg)	65.4±6.6	65.3±6.8	64.5±6.9	69.4±7.5†
MBPpwv(mmHg)	92±10	94±11†	89±9	93±10†
HR (beats/min)	64±10	65±10†	64±10	66±10†
TC (nmol/L)	5.0±0.8	5.2±0.8†	4.8±0.8	5.2±0.9†
HDL (nmol/L)	1.5±0.3	1.5±0.4	1.5±0.3	1.5±0.3
TG (nmol/L)	1.3±0.8	1.3±0.9	1.0±0.87	1.4±0.8†
FPG (nmol/L)	5.2±0.8	5.1±0.8	5.0±0.45	5.1±0.5
baPWV (cm/s)	1,248±184	1,286±184†	1,221±181	1,266±180†
Smoking (*n*)	496	428	114	95

Overweight ($n=502$)

	Weight change			
	Gain <5% ($n=430$)		Gain ≥5% ($n=72$)	
	Baseline	Year 3	Baseline	Year 3
Age	42±8		36±5	
Weight (kg)	77.6±6.6	77.2±6.6	77.1±6.4	82.5±6.9†
MBPpwv (mmHg)	96±11	99±12†	94±8	99±11†
HR (beats/min)	66±10	67±10†	66±10	67±9
TC (nmol/L)	5.3±0.8	5.4±0.9†	5.0±0.8	5.4±0.8†
HDL (nmol/L)	1.3±0.3	1.4±0.3†	1.2±0.2	1.2±0.2
TG (nmol/L)	1.7±1.3	1.7±1.1	1.5±0.9	2.1±1.4†
FPG (nmol/L)	5.3±0.6	5.3±0.8	5.2±0.5	5.1±0.5
baPWV (cm/s)	1,278±179	1,316±185†	1,232±175	1,303±205†
Smoking (*n*)	192	171	27	22

Obese ($n=50$)

	Weight change			
	Gain <5% ($n=43$)		Gain ≥5% ($n=7$)	
	Baseline	Year 3	Baseline	Year 3
Age	40±8		35±6	
Weight (kg)	93.5±10.2	92.1±11.2*	94.0±10.8	101.2±12.2†
MBPpwv (mmHg)	101±9	104±12	103±15	113±16†
HR (beats/min)	67±10	69±11	68±11	75±15
TC (nmol/L)	5.5±1.2	5.5±1.1	5.7±0.6	6.0±0.5*
HDL (nmol/L)	1.2±0.3	1.3±0.3	1.4±0.4	1.3±0.3
TG (nmol/L)	2.4±2.5	2.3±1.9	1.4±0.4	1.9±0.9
FPG (nmol/L)	5.3±0.7	5.4±1.0	4.9±0.4	5.0±0.3
baPWV (cm/s)	1,256±174	1,324±196†	1,311±190	1,390±201†
Smoking (*n*)	21	18	5	5

Gain <5%, subjects without weight gain; Gain ≥5%, subjects with weight gain; MBPpwv, mean blood pressure obtained at the time of the brachial-ankle pulse wave velocity measurement; HR, heart rate obtained at the time of the brachial-ankle pulse wave velocity measurement; TC, plasma levels of total cholesterol; HDL, plasma levels of high density-lipoprotein cholesterol; TG, plasma levels of triglycerides; FPG, fasting plasma glucose; baPWV, brachial-ankle pulse wave velocity; Smoking, number of subjects who smoked. *$p<0.05$, †$p<0.01$, for year 3 *vs.* baseline.

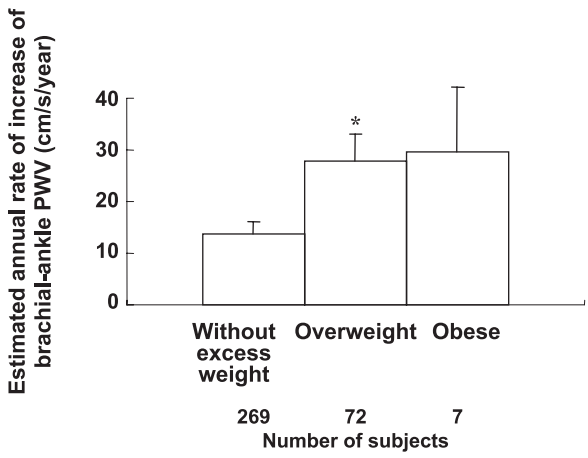

Fig. 2. *Adjusted values of estimated mean annual rate of increase in brachial-ankle pulse wave velocity in subjects with weight gain among the without excess weight, overweight and obese groups. Gain ≥5%, subjects with weight gain; gain <5%, subjects without weight gain. *p<0.05 vs. subjects without excess weight.*

study was 27 kg/m^2) (*8*). Thus, further study was needed to clarify the association between baseline BMI classifications and arterial stiffening associated with weight gain. The subjects of the present study were healthy middle-aged Japanese men, and more than half of them were categorized as without excess weight (the mean BMI of the present study was 23.5 kg/m^2). The ARbaPWV in subjects with weight gain was higher than that in subjects without weight gain among the overweight group but not among the without excess weight or obese groups. The number of subjects with weight gain in the obese group was relatively low, but the ARbaPWV was similar between the with (overweight plus obese) and without excess weight groups. Therefore, while the present study could not determine whether weight gain accelerated arterial stiffening in obese subjects, weight gain seemed to accelerate arterial stiffening in overweight subjects, but not in subjects without excess weight.

Increased arterial stiffness increases cardiovascular risk *via* several mechanisms, such as increased cardiac afterload, impaired coronary blood supply, cardiac diastolic dysfunction caused by ventriculo-arterial coupling, or direct atherogenic actions (*4*, *14*). The present study suggested that weight gain may increase the cardiovascular risk related to arterial stiffness in overweight subjects but not in subjects without excess weight. The risk of cardiovascular events increases along with an increasing BMI classification. Although weight gain further increases such risks (*1*–*3*), whether the BMI classifications themselves modify the increased risk associated with weight gain is unclear. The results of the present study suggested that the increase in cardiovascular risk associated with weight gain was larger in the overweight group than in the without excess weight group. In addition, while the prevention of weight gain is an important public health issue (*15*), some studies have expressed concern about the feasibility of preventing weight gain (*16*, *17*). Considering the results of the present study, approaches to preventing further weight gain in overweight subjects should be established.

Several mechanisms, including the exaggeration of conventional risk factors (elevated blood pressure and abnormal glucose and/or lipid metabolisms), the activation of the sympathetic nervous system, the impairment of nitric oxide activity, and/or abnormal conditions of vascular smooth muscle cells and vascular connective tissues, have been proposed to explain arterial stiffening associated with weight gain (*9*, *10*). In the present study, the effects of weight gain on elevated blood pressure and abnormalities in glucose and lipid metabolism were similar among the without excess weight and overweight groups. Weight gain induces abnormalities in the production/release of atherogenic adipocytokines, which, in turn, increase arterial stiffness (*9*, *14*). These cytokines are produced and released from visceral adipose tissues (*18*). The amount of visceral adipose tissue is larger in the overweight subjects than in the without excess weight subjects (*19*). Therefore, these factors may contribute, at least in part, to the accelerated arterial stiffening associated with weight gain in overweight subjects.

Study Limitations

This study had three major limitations. First, brachial-ankle PWV, not carotid-femoral PWV, was used, even though carotid-femoral PWV is a better established method of assessing central arterial stiffness. While brachial-ankle PWV includes peripheral muscular arterial stiffness, it has also been shown to be closely correlated with the aortic PWV (*12*). Furthermore, recent studies have demonstrated that this parameter can be used as a marker to predict future cardiovascular events (*20*, *21*). Second, the results of this study were not confirmed in female subjects or in subjects of other ethnicities. In addition, Wildman *et al*. demonstrated that the increase in arterial stiffness associated with a higher BMI was blunted in subjects who were more than ≥60 years old (*22*). Therefore, further studies are needed to determine whether the effect of percent changes in body weight on the annual rate of arterial stiffening might be modified in subjects over the age of 60 years. And third, the small number of obese subjects in the present study prevented us from determining whether weight gain accelerates arterial stiffening in obese subjects.

Conclusion

Our study revealed that the BMI classifications modified the annual rate of increase in arterial stiffening associated with weight gain. Weight gain seems to accelerate arterial stiffening in overweight subjects but not in those without excess weight. Weight gain in overweight subjects seemed to worsen the cardiovascular risk related to arterial stiffness in healthy

middle-aged Japanese men. Thus, the prevention of weight gain should be emphasized in overweight subjects.

References

1. Kannel WB, D'Agostino RB, Cobb JL: Effect of weight on cardiovascular disease. *Am J Clin Nutr* 1996; **63** (3 Suppl): 419S–422S.
2. Overweight, obesity, and health risk. National Task Force on the Prevention and Treatment of Obesity. *Arch Intern Med* 2000; **160**: 898–904.
3. Poirier P, Giles TD, Bray GA, *et al*: Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss. *Arterioscler Thromb Vasc Biol* 2006; **26**: 968–976.
4. Safar ME, Levy BI, Struijker-Boudier H: Current perspectives on arterial stiffness and pulse pressure in hypertension and cardiovascular diseases. *Circulation* 2003; **107**: 2864–2869.
5. Willum-Hansen T, Staessen JA, Torp-Pedersen C, *et al*: Prognostic value of aortic pulse wave velocity as index of arterial stiffness in the general population. *Circulation* 2006; **113**: 664–670.
6. Zebekakis PE, Nawrot T, Thijs L, *et al*: Obesity is associated with increased arterial stiffness from adolescence until old age. *J Hypertens* 2005; **23**: 1839–1846.
7. Toto-Moukouo JJ, Achimastos A, Asmar RG, Hugues CJ, Safar ME: Pulse wave velocity in patients with obesity and hypertension. *Am Heart J* 1986; **112**: 136–140.
8. Wildman RP, Farhat GN, Patel AS, *et al*: Weight change is associated with change in arterial stiffness among healthy young adults. *Hypertension* 2005; **45**: 187–192.
9. Safar ME, Czernichow S, Blacher J: Obesity, arterial stiffness, and cardiovascular risk. *J Am Soc Nephrol* 2006; **17** (4 Suppl 2): S109–S111.
10. Seals DR, Gates PE: Stiffening our resolve against adult weight gain. *Hypertension* 2005; **45**: 175–177.
11. Tomiyama H, Hashimoto H, Hirayama Y, *et al*: Synergistic acceleration of arterial stiffening in the presence of raised blood pressure and raised plasma glucose. *Hypertension* 2006; **47**: 180–188.
12. Yamashina A, Tomiyama H, Takeda K, *et al*: Validity, reproducibility, and clinical significance of noninvasive brachial-ankle pulse wave velocity measurement. *Hypertens Res* 2002; **25**: 359–364.
13. Wannamethee SG, Shaper AG, Walker M: Overweight and obesity and weight change in middle aged men: impact on cardiovascular disease and diabetes. *J Epidemiol Community Health* 2005; **59**: 134–139.
14. Zieman SJ, Melenovsky V, Kass DA: Mechanisms, pathophysiology, and therapy of arterial stiffness. *Arterioscler Thromb Vasc Biol* 2005; **25**: 932–943.
15. Kopelman P: Health risks associated with overweight and obesity. *Obes Rev* 2007; **8** (Suppl 1): 13–17.
16. Levine MD, Klem ML, Kalarchian MA, *et al*: Weight gain prevention among women. *Obesity* 2007; **15**: 1267–1277.
17. Jakicic JM, Otto AD: Physical activity considerations for the treatment and prevention of obesity. *Am J Clin Nutr* 2005; **82** (1 Suppl): 226S–229S.
18. Matsuzawa Y: Therapy Insight: adipocytokines in metabolic syndrome and related cardiovascular disease. *Nat Clin Pract Cardiovasc Med* 2006; **3**: 35–42.
19. Lo J, Dolan SE, Kanter JR, *et al*: Effects of obesity, body composition, and adiponectin on carotid intima-media thickness in healthy women. *J Clin Endocrinol Metab* 2006; **91**: 1677–1682.
20. Tomiyama H, Koji Y, Yambe M, *et al*: Brachial–ankle pulse wave velocity is a simple and independent predictor of prognosis in patients with acute coronary syndrome. *Circ J* 2005; **69**: 815–822.
21. Kitahara T, Ono K, Tsuchida A, *et al*: Impact of brachial-ankle pulse wave velocity and ankle-brachial blood pressure index on mortality in hemodialysis patients. *Am J Kidney Dis* 2005; **46**: 688–696.
22. Wildman RP, Mackey RH, Bostom A, Thompson T, Sutton-Tyrrell K: Measures of obesity are associated with vascular stiffness in young and older adults. *Hypertension* 2003; **42**: 468–473.