Obesity is associated with increased arterial stiffness from adolescence until old age

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Objective **To our knowledge, only two previous studies have investigated the age dependence of the relationship between the characteristics of large arteries and excessive body weight. We therefore investigated whether the relationship between arterial stiffness and body mass index (BMI) was consistent across an age range from 10 to 86 years.**

Methods **Using a cross-sectional population-based design, we randomly recruited 1306 individuals (median age 43.9 years; 50.5% women). Using a wall-tracking ultrasound system, we measured the properties of the carotid, femoral and brachial arteries and carotid–femoral pulse wave velocity. We analysed men and women separately while adjusting for significant covariates, including age, mean arterial pressure, heart rate, current smoking, alcohol intake and use of antihypertensive drugs.**

Results **Before and after adjustment, arterial diameter increased with BMI in all territories, with an opposite trend for arterial distensibility. In men and women, the relationships of brachial and femoral properties with BMI were consistent across the whole age range. In men and women, carotid distensibility decreased more with BMI at young than old age. In middle-aged and older women, but not in men of any age, pulse wave velocity increased with higher BMI.**

Conclusions **Across a wide age range, the diameter and stiffness of muscular arteries increased with higher BMI. In elastic arteries, the relationship between arterial stiffness and BMI was more complex and varied with sex and age. The mechanisms underlying the influence of adiposity on the properties of muscular and elastic arteries and the reversibility of these associations by weight reduction at young age need further clarification.** ***J Hypertens*** **23:1839–1846 © 2005 Lippincott Williams & Wilkins.**

Journal of Hypertension 2005, **23**:1839–1846

Keywords: aging, arterial compliance, arterial distensibility, arterial stiffness, body mass index, obesity

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Sponsorship: The European Union (IC15-CT98-0329-EPOGH and QLGI-CT-2000-01137-EURNETGEN), the Fonds voor Wetenschappelijk Onderzoek Vlaanderen, Brussels, Belgium (G.0291.98, G.0424.03 and G.0256.05), and the University of Leuven, Belgium (OT/99/28 and OT/04/34) provided research grants in support of the FLEMENGHO study.

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Received 2 February 2005 **Revised** 16 June 2005
Accepted 17 June 2005

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Introduction

Worldwide, the prevalence of overweight and obesity has reached pandemic proportions [1,2]. In the United States and western Europe, adiposity substantially adds to the cardiovascular risk of 60% of adults and 10% of youth. Obesity is associated with impaired function of the large arteries, which might be the consequence of metabolic dysregulation, inflammatory pathways, obstructive sleep apnoea, or other mechanisms [3,4]. However, to our knowledge, only two previous studies [5,6] have investigated the age dependence of the relationship between the characteristics of the large arteries and excessive body weight. In a cross-sectional study of 363 adults aged 20–77 years, Wildman and colleagues [6], while adjusting for age and other confounders, noticed positive associations between aortic pulse wave velocity and various measures of obesity. In a prospective study of 159 pubertal adolescents followed up for over 20 years and in a cross-sectional analysis of 336 subjects aged 36 years, Ferreira and coworkers [5] found that the stiffness of several large arteries increased with obesity.

In the framework of the Flemish Study on Environment, Genes and Health Outcomes (FLEMENGHO), we used the same ultrasound technique as in the study by Ferreira *et al*. [5] to collect complex vascular phenotypes in 1306

individuals with a wide age range, who were randomly recruited from the population [7]. Here, we report the combined influences of body mass index (BMI) and age on vascular structure and function.

Methods

Study population

The FLEMENGHO study [7] involves a random sample of families living in a defined geographical area in northern Belgium. Eligible offspring were at least 10 years old. The Ethics Committee of the University of Leuven approved the study. All participants or their parents gave informed written consent. The participation rate averaged 64.3%.

Clinical measurements

For at least 3 h before being examined, the participants refrained from heavy exercise, smoking, alcohol or caffeine-containing beverages. Trained nurses measured blood pressure and anthropometric characteristics. They administered a questionnaire to collect information about each subject's medical history, smoking and drinking habits, and intake of medications. Each participant's office blood pressure was the average of five consecutive readings. BMI was defined as weight in kilograms divided by the square of height in metres. Normal weight, overweight and obesity corresponded with ranges of BMI of less than 25 kg/m^2, 25–30 kg/m^2 and 30 kg/m^2 or greater, respectively. We measured blood glucose and total and high-density lipoprotein (HDL)-cholesterol on a venous blood sample by standard biochemical methods.

Vascular measurements

By means of a pulsed ultrasound wall-tracking system (Wall Track System; Pie Medical, Maastricht, the Netherlands), three trained researchers (E.J.B., J.J.H-S., and T.N.) obtained vascular measurements at the common carotid artery 2 cm proximal of the carotid bulb, at the femoral artery 1 cm proximal of the bifurcation into the profound and superficial branches, and at the right brachial artery 2 cm proximal of the antecubital fossa [7]. The observers also determined carotid–femoral pulse wave velocity from the length of the carotid–femoral segment and the transit time of the pulse wave. The carotid–femoral segment was the difference of the distances between the site of the carotid ultrasound measurement and the suprasternal notch and between the suprasternal notch and the site of the femoral measurement.

During the ultrasound examination, an automated oscillometric device (Dinamap 845; Critikon Inc., Tampa, Florida, USA) recorded blood pressure at the upper arm at 5-min intervals. As for the conventional auscultatory measurements, cuff size was adjusted to the circumference of the upper arm [8]. Standard cuffs had an inflatable bladder of 12 cm × 24 cm. If the arm circumference exceeded 31 cm, larger cuffs with a bladder of 15 cm × 35 cm were utilized. As described elsewhere [9], the observers applied applanation tonometry with a pencil-shaped probe (Millar Instruments Inc., Houston, Texas, USA) and calibration to mean and diastolic pressure at the brachial artery to derive the local pulse pressure at the other arteries. We computed cross-sectional compliance (CC) and the distensibility coefficient (DC) from the diastolic cross-sectional area (A), the systolic increase in cross-sectional area (ΔA) and the local pulse pressure (ΔP) [10]: $CC = \Delta A/\Delta P$ and $DC = (\Delta A/A)/\Delta P$. A and ΔA were calculated as $A = \pi \times (D/2)^2$ and $\Delta A = \pi \times [(D + \Delta D)/2]^2 - \pi \times (D/2)^2$.

Statistical analysis

For database management and statistical analysis, we used SAS software version 8.2 (SAS Institute Inc., Cary, North Carolina, USA). We analysed women and men separately. We compared means, medians and proportions by means of a large sample z-test, Wilcoxon's test and the χ^2 statistic, respectively. Our statistical methods also included single and multiple linear regression. For the clarity of presentation and to allow comparison with other reports [6], we subdivided participants according to median age. However, we only used continuous distributions to explore the interaction between BMI and age in relation to the vascular properties.

Significant covariates of the vascular measurements were traced by a stepwise regression procedure, terminating when all partial regression coefficients were significant at 5%. Covariates considered for entry into the model were observer, age, BMI, pulse rate, mean arterial pressure, current smoking, alcohol intake and the use of antihypertensive drugs. In sensitivity analyses, we forced additional covariates in the models, including blood glucose and serum total and HDL-cholesterol, and in women also the use of oral contraceptives and hormonal replacement therapy. We also repeated the analyses with patients on antihypertensive treatment excluded.

Results

Characteristics of participants

The median age of the 1306 participants, 646 men and 660 women, was 43.9 years (range 10–86 years). Table 1 summarizes their demographic characteristics. In smokers, median tobacco use was 18 cigarettes a day (10th to 90th percentile interval, 6–30). In drinkers, median alcohol consumption was 20 g a day (10–50 g). Among 412 premenopausal and 248 postmenopausal women, 76 (18.5%) and 13 (5.2%) used oral contraceptives or hormonal replacement therapy, respectively.

Vessel wall properties in relation to body mass index

Table 2 gives the vessel wall properties by sex and vascular territory. Figure 1 illustrates the association

Table 1 Characteristics of participants by sex

Variable name	Women ($n = 660$)	Men ($n = 646$)
Demographic characteristics		
Age (years)	44.2 ± 15.8	44.9 ± 15.4
Body mass index (kg/m^2)	24.9 ± 4.6	25.7 ± 3.8
Systolic pressure (mmHg)[a]	117.7 ± 14.8	125.2 ± 13.1
Diastolic pressure (mmHg)[a]	70.4 ± 8.9	74.3 ± 8.9
Pulse rate (beats per minute)	64.3 ± 9.1	60.3 ± 10.0
Numbers with characteristics (%)		
Body mass index 25–30 kg/m^2	185 (28.0)	296 (45.8)
Body mass index ≥ 30 kg/m^2	93 (14.0)	80 (12.4)
Smokers	202 (31.3)	180 (27.3)
Drinkers	196 (29.7)	362 (56.0)
Antihypertensive therapy	95 (14.4)	86 (13.3)
Biochemical measurements		
Glucose (mmol/l)	5.34 ± 1.22	5.47 ± 1.70
Cholesterol total (mmol/l)	5.33 ± 1.06	5.32 ± 1.06
HDL-cholesterol (mmol/l)	1.64 ± 0.42	1.31 ± 0.35

Unless indicated otherwise, values are means ± SD. Sex differences were significant ($P < 0.01$) with exception of age ($P = 0.46$), current smoking ($P = 0.11$), use of antihypertensive drugs ($P = 0.57$), blood glucose ($P = 0.15$), and total cholesterol ($P = 0.91$). [a]Average of five auscultatory readings at the brachial artery obtained at the examination centre. HDL, high-density lipoprotein.

between carotid, brachial and femoral diameter and BMI across sex and age group-specific quartiles of the distribution of BMI. Similar information for the distensibility coefficients appears in Figure 2.

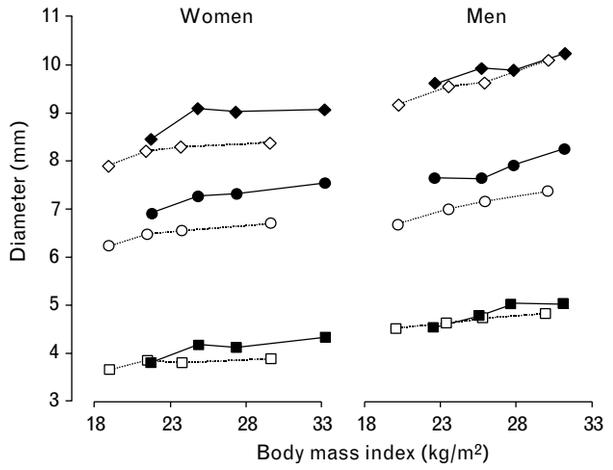
Before (Fig. 1) and after adjustment for observer, age, mean arterial pressure, pulse rate, current smoking, alcohol intake and the use of antihypertensive drugs, arterial diameter significantly increased with BMI in the three vascular territories in women as well as in men (Table 3). Arterial distensibility consistently decreased with BMI (Table 3). With similar adjustments applied, the carotid–femoral pulse wave velocity increased with higher BMI in women, but not in men (Table 3).

Table 2 Arterial wall properties by sex

Variable name	Women ($n = 660$)	Men ($n = 646$)
Carotid–femoral pulse wave velocity (m/s)	6.31 ± 2.09	6.56 ± 2.09
Common carotid artery		
Diameter (mm)	6.83 ± 0.81	7.58 ± 0.94
Distension (μm)	491.5 ± 191.9	537.8 ± 208.2
Pulse pressure (mmHg)	46.7 ± 12.3	49.2 ± 13.3
Distensibility coefficient (10^{-3}/kPa)	26.7 ± 14.1	24.2 ± 11.9
Compliance coefficient (mm^2/kPa)	0.95 ± 0.44	1.06 ± 0.45
Brachial artery		
Diameter (mm)	3.90 ± 0.71	4.80 ± 0.72
Distension (μm)	154.2 ± 116.4	175.5 ± 126.7
Pulse pressure (mmHg)	47.1 ± 10.0	50.6 ± 10.2
Distensibility coefficient (10^{-3}/kPa)	13.8 ± 12.0	12.1 ± 12.0
Compliance coefficient (mm^2/kPa)	0.15 ± 0.12	0.20 ± 0.15
Femoral artery		
Diameter (mm)	8.50 ± 1.16	9.94 ± 1.46
Distension (μm)	290.5 ± 148.2	312.4 ± 185.0
Pulse pressure (mmHg)	50.8 ± 13.0	54.4 ± 13.2
Distensibility coefficient (10^{-3}/kPa)	11.5 ± 7.3	9.5 ± 6.0
Cross-sectional compliance (mm^2/kPa)	0.63 ± 0.38	0.73 ± 0.47

Values are means ± SD. All sex differences were statistically significant ($P < 0.02$).

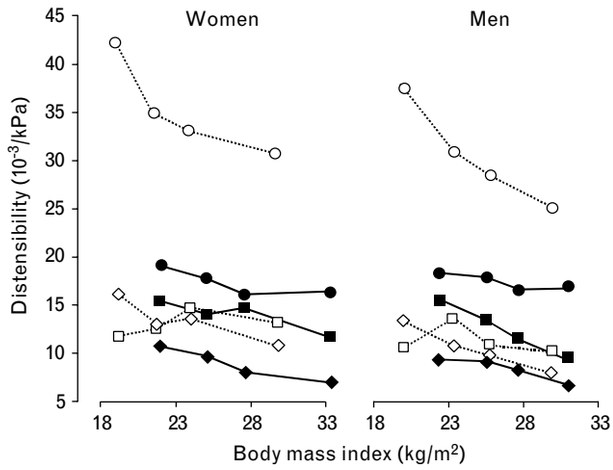
Fig. 1



Arterial diameter by sex and vascular territory. Plotted values are means in sex and age group-specific quartiles of body mass index. Age groups < 40 years: Common carotid artery (CCA) ·····○·····; brachial artery (BA) ·····□·····; femoral artery (FA) ·····◇·····; ≥ 40 years: CCA ——●——; BA ——■——; FA ——◆——.

There was no heterogeneity between women and men in the relationship of arterial diameter or distensibility with BMI ($0.17 < P < 0.92$). The latter measurement incorporates weight and height. In a further analysis (Fig. 3), we therefore pooled the two sexes and we replaced in the multiple regression models BMI by weight and height. Arterial diameter and distensibility were significantly ($P < 0.008$) associated with body weight as well as body height in the three vascular

Fig. 2



Arterial distensibility by sex and vascular territory. Plotted values are means in sex and age group-specific quartiles of body mass index. Age groups < 40 years: Common carotid artery (CCA) ·····○·····; brachial artery (BA) ·····□·····; femoral artery (FA) ·····◇·····; ≥ 40 years: CCA ——●——; BA ——■——; FA ——◆——.

Table 3 Partial regression coefficients between vessel wall properties and body mass index by sex

	Women ($n = 660$)			Men ($n = 646$)		
Measurement	Coefficient ± SE	P	P_{int}	Coefficient ± SE	P	P_{int}
Carotid–femoral PWV (m/s)	0.038 ± 0.016	0.02	0.14	−0.011 ± 0.021	0.58	0.16
Common carotid artery						
Diameter (mm)	0.020 ± 0.006	0.0006	0.004	0.051 ± 0.008	0.0001	0.08
Distensibility (10^{-3}/kPa)	−0.172 ± 0.078	0.027	0.0001	−0.372 ± 0.097	0.0001	0.001
Brachial artery						
Diameter (mm)	0.022 ± 0.005	0.0001	0.07	0.054 ± 0.009	0.0001	0.79
Distensibility (10^{-3}/kPa)	−0.156 ± 0.069	0.02	0.49	−0.329 ± 0.077	0.0001	0.57
Femoral artery						
Diameter (mm)	0.037 ± 0.009	0.0002	0.66	0.088 ± 0.016	0.0001	0.07
Distensibility (10^{-3}/kPa)	−0.211 ± 0.065	0.001	0.17	−0.245 ± 0.066	0.0002	0.76

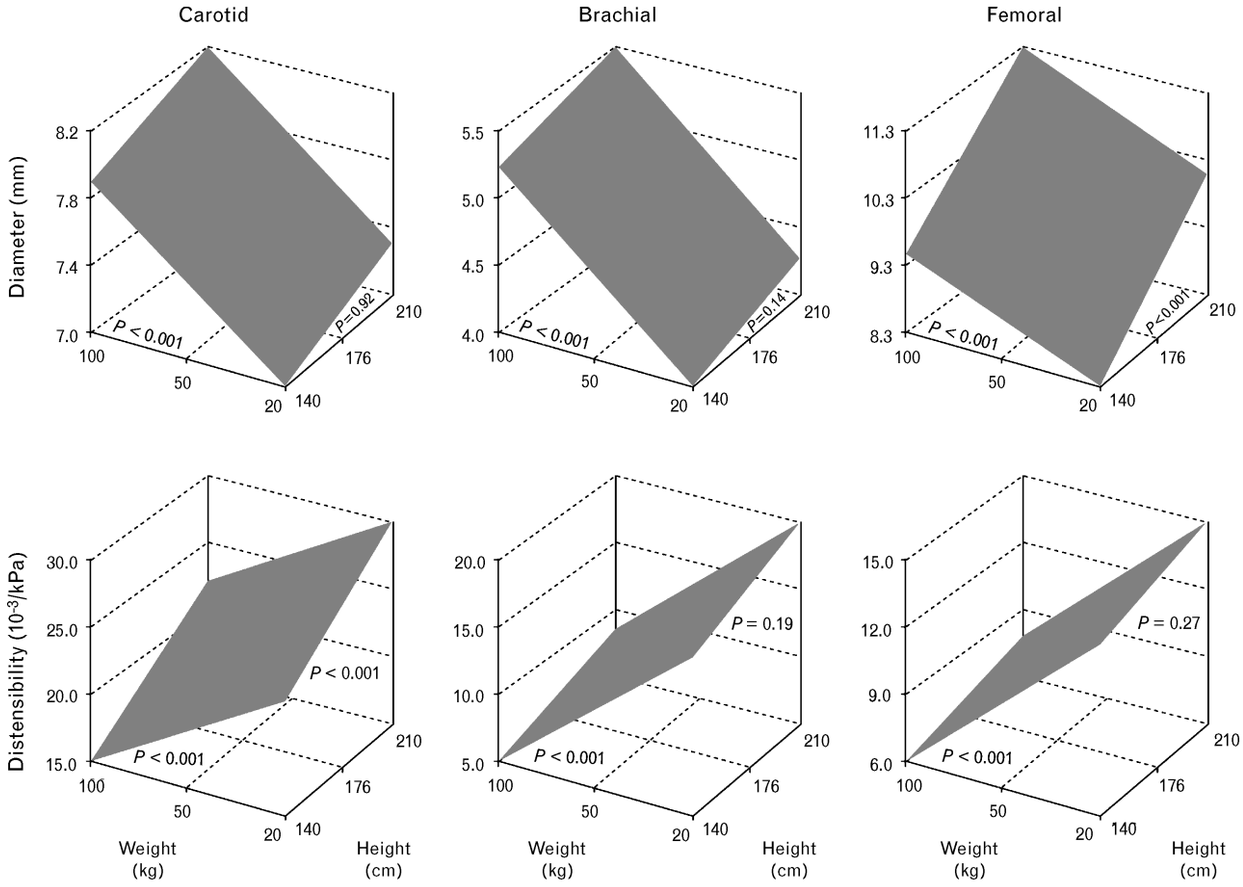
PWV, Pulse wave velocity. Regression coefficients were adjusted for observer, age, mean arterial pressure, pulse rate, smoking, alcohol intake, and antihypertensive drug intake. P and P_{int} refer to the significance of the partial regression coefficient with body mass index and the continuous interaction term between body mass index and age, respectively.

territories, with the exception of the relationship of body height with carotid ($P = 0.92$) and brachial ($P = 0.14$) diameter as well as with brachial ($P = 0.19$) and femoral ($P = 0.27$) distensibility.

Interaction between body mass index and age

With similar adjustments as before, we explored the interaction between BMI and age using continuous variables (Table 3). These interaction terms were either

Fig. 3



Relationship between arterial characteristics and body weight and height in men and women combined. The relationships were standardized for observer, age, mean arterial pressure, pulse pressure, smoking, alcohol intake, and use of antihypertensive drugs.

Table 4 Changes in arterial characteristics associated with a 1 SD increase in body mass index at specific ages

Measurement	Age	Women	Men
Carotid–femoral PWV (m/s)	20	0.017 (−0.203 to 0.237)	−0.193 (−0.454 to 0.068)
	40	0.140 (0.015 to 0.265)	−0.053 (−0.216 to 0.110)
	60	0.263 (0.073 to 0.453)	0.087 (−0.158 to 0.332)
Common carotid artery			
Diameter (mm)	20	−0.022 (−0.036 to −0.008)	0.127 (0.017 to 0.237)
	40	0.063 (0.016 to 0.110)	0.194 (0.127 to 0.261)
	60	0.148 (0.083 to 0.213)	0.262 (0.172 to 0.352)
Distensibility (10^{-3}/kPa)	20	−2.623 (−3.707 to −1.539)	−3.102 (−4.335 to −1.869)
	40	−0.980 (−1.599 to −0.361)	−1.640 (−2.397 to −0.883)
	60	0.633 (−0.239 to 1.505)	−0.178 (−1.270 to 0.914)
Brachial artery			
Diameter (mm)	20	0.035 (0.034 to 0.104)	0.225 (0.137 to 0.313)
	40	0.079 (0.040 to 0.118)	0.217 (0.164 to 0.270)
	60	0.123 (0.072 to 0.174)	0.208 (0.135 to 0.281)
Distensibility (10^{-3}/kPa)	20	−0.322 (−1.341 to 0.697)	−1.079 (−2.092 to −0.066)
	40	−0.564 (−1.134 to 0.006)	−1.284 (−1.900 to −0.669)
	60	−0.806 (−1.551 to −0.061)	−1.490 (−2.333 to −0.647)
Femoral artery			
Diameter (mm)	20	0.122 (−0.013 to 0.257)	0.496 (0.296 to 0.696)
	40	0.144 (0.066 to 0.222)	0.362 (0.239 to 0.485)
	60	0.166 (0.050 to 0.282)	0.228 (0.044 to 0.412)
Distensibility (10^{-3}/kPa)	20	−1.348 (−2.228 to −0.468)	−1.079 (−1.914 to −0.244)
	40	−0.914 (−1.429 to −0.399)	−0.984 (−1.501 to −0.467)
	60	−0.480 (−1.205 to 0.245)	−0.888 (−1.647 to −0.129)

PWV, Pulse wave velocity. Effect sizes (95% confidence interval) are for an increase in body mass index by 4 kg/m^2 (~1 SD). Estimates account for the covariance between age and body mass index and for other covariates, including observer, age, mean arterial pressure, pulse rate, smoking, alcohol intake, and antihypertensive drug intake. *P* values for the continuous interaction term between body mass index and age are presented in Table 3.

non-significant or of only borderline significance ($0.05 < P < 0.10$), except for carotid diameter in women and carotid distensibility in both sexes ($P \leq 0.004$).

Table 4 provides the predicted effect sizes, which in women and men were associated with an increase in BMI by 4.0 kg/m^2 (~1 SD) at ages 20, 40 or 60 years. These adjusted estimates accounted for other covariates and for the interaction and covariance between BMI and age. Brachial and femoral diameter and distensibility changed with BMI in a directionally consistent manner across the whole age range. In men and women, carotid distensibility decreased more with body mass at younger than at older age. In middle-aged and older women, pulse wave velocity increased with higher BMI. In men, the associations between pulse wave velocity and BMI were not significant, irrespective of age.

Neither in women nor men was cross-sectional compliance in any vascular territory significantly and independently correlated with BMI (data not shown). Further cumulative adjustment of the vascular measurements for total and HDL-cholesterol and blood glucose, and in women also for the use of oral contraceptives or hormonal replacement therapy, did not materially alter our results. Analyses with subjects on antihypertensive treatment excluded were also confirmatory.

Discussion

The key finding of our study was that from 10 to 86 years in women as well as men the diameter and stiffness of the muscular brachial and femoral arteries consistently increased with higher BMI. Age did not significantly impact on the relationship of the characteristics of the muscular arteries with BMI. In contrast, in women and men, stiffening of the carotid artery with BMI was more pronounced at younger than older age. In middle-aged and older women, but not in men of any age, pulse wave velocity increased with higher BMI.

Across three vascular beds and two sexes, at all ages, the arterial lumen consistently increased with higher BMI. In experimental animals and humans, weight gain leads to expansion of the extracellular volume and increases cardiac output and regional blood flow to adipose as well as non-adipose tissues [4,11]. The mechanisms responsible for the increased regional blood flow remain to be elucidated, but must involve the system-wide increased metabolic rate, local accumulation of vasoactive metabolites [12], and the growth of organs and tissues, which have to sustain a larger body with higher metabolic needs. These haemodynamic features, shear stress, increased blood pressure and various nervous and hormonal mechanisms can explain the inverse functional association between arterial distensibility and obesity, which in the long run may lead to structural adaptations in the arteries [4,13,14]. We did not find any association between cross-sectional compliance and BMI, possibly because the computation of this vascular index does not account for the diastolic lumen diameter, which was larger in obese than in non-obese individuals.

Among the studies that investigated to what extent adiposity might impact on the properties of large arteries

[5,6,11,15–26], most had a small sample size (range 16 [22] to 75 [15]; median, 46 [16]) with a case–control design involving obese and non-obese healthy individuals [11,15–17,20–22] or obese and non-obese patients with hypertension [11,19] or type 2 diabetes [25]. Few studies were population based and had sufficient statistical power to allow conclusions with relevant external validity [5,6,18,23,24,26]. Most researchers determined central or peripheral pulse wave velocity [5,6,18,19, 23–26]. Other investigators used the ratio of pulse pressure to stroke index [11], the ratio of pulse pressure to the systolic increase in the aortic cross-sectional area [16], or the central systolic augmentation index [22]. Few researchers measured cross-sectional compliance or distensibility at the radial artery [20], the common carotid artery [15], the carotid and femoral arteries [17], or as in the present study at three different arteries [5,21]. By and large, most studies demonstrated that the stiffness of the large arteries increased with various indices of adiposity, including BMI.

Two approaches can shed light on the age at which BMI starts influencing the properties of large arteries. First, some researchers specifically recruited children [27] or young adults [5,16,17,20,22,23] with mean ages ranging from 12.4 [15] to 36.0 [5] years. Among these reports [5,15–17,20,22,23], four studies with a case–control design demonstrated increased arterial stiffness in obese subjects [15,16,20,22]. However, in three studies, the continuous relationship between measures of stiffness and obesity were only significant because either obese and non-obese subjects [20,22] or men and women [17] were pooled. In one large study [23], the relationship between pulse wave velocity and BMI did not reach statistical significance. Among the studies in young adults, the report by Ferreira and colleagues [5] stands out. It integrated cross-sectional and prospective findings. It included various indices of obesity and the bodily distribution of fat tissue as well as comprehensive measurements of the arterial properties in the same four vascular territories as in the present study. Ferreira and colleagues [5] found that truncal subcutaneous fat accumulation in adolescents was an independent predictor of increased vascular stiffness at age 36 years. Moreover, at age 36 years, arterial stiffness was positively and independently associated with the amount of abdominal and truncal subcutaneous fat.

Recruitment of study participants with a wide age range, as in the present study, constitutes a second approach, which allows an investigation of the age dependency of the association between arterial properties and adiposity. Among the population-based studies with an appropriate age range [6,24,26], only Wildman and coworkers [6] expanded their analyses along these lines. Pulse wave velocity strongly correlated with higher body weight, BMI and the waist-to-hip ratio, independent of age, sex, race and systolic blood pressure. Even among young adults with an age range from 20 to 30 years, subjects with a BMI exceeding 30 kg/m^2 had a mean aortic pulse wave velocity that was 0.047 m/s higher than in their non-obese counterparts. The analysis of Wildman *et al.* [6] was not stratified for sex.

In the present study, BMI was a significant and independent determinant of pulse wave velocity in women, but not in men. In 521 healthy participants of the Framingham Heart Study with mean age of 56.6 years (63.9% women), neither carotid–femoral nor carotid–brachial pulse wave velocity were related to BMI [24]. This was also the case in 2431 Japanese men (aged 35–54 years) [26] and 524 Dutch men and women (aged 27–30 years) [23]. The Framingham investigators excluded obese ($\geq$ 30 kg/m^2) individuals from their analysis. BMI in the Japanese [26] and Dutch [23] studies averaged only 23.4 and 24.5 kg/m^2, respectively. Nevertheless, our population study and at least three others [23,24,26] suggest that the age-adjusted relationship between aortic stiffness and adiposity might be weaker than for peripheral arteries. Obesity in men is more centrally located than in women. An overestimation of the length of the carotid–femoral segment can artificially inflate the measurement of aortic pulse wave velocity. However, such artefact would strengthen rather than weaken the correlations with BMI. Two other mechanisms are probably more plausible to explain the weak relationship between aortic pulse wave velocity and BMI. First, BMI explains up to 30% of the blood pressure variability in the general population. Pulse wave velocity is measured independently of blood pressure, whereas the computation of arterial distensibility involves blood pressure. Second, BMI is an imprecise measure of adiposity. In 2488 older adults with a mean age of 74 years (52.3% women) enrolled in the Study of Health, Aging and Body Composition [18], the researchers used computed tomography to measure abdominal visceral fat. In that population-based study, the investigators noticed in all subjects and even in thirds of the distribution of body weight a strong association between aortic pulse wave velocity and abdominal visceral fat, which was independent of body weight, whereas the association between pulse wave velocity and body weight was not significant when controlling for other covariates [18].

The present study has to be interpreted within the context of its limitations and strengths. We did not assess body fatness and its distribution by means of sophisticated techniques, such as dual energy X-ray absorptiometry [5,18,25] or computed tomography [18,25], but as most other researchers, we estimated adiposity from simple anthropometric measurements. We applied a cross-sectional design to investigate the influence of age on the relationship between vascular stiffness and obesity. We cannot exclude the possibility that cohort

effects or secular trends over the observation period (1999–2003) confounded our results. Most subjects were examined in a non-fasting state. The requested 3-h interval of abstinence from drinking alcoholic or caffeine-containing beverages or heavy exercise might not have been long enough to standardize the vascular measurements fully. We did not collect information on obstructive sleep apnoea, which is common among obese individuals and which itself might affect cardiac and vascular function [3]. The prevalence of sleep apnoea in middle-aged American and western European populations is approximately 20%, which is less than the prevalence of overweight and obesity. Approximately 40% of obese individuals experience sleep apnoea [28]. Obstruction of the airways during sleep might therefore have been a confounder in the presently reported associations between the arterial properties and BMI. On the other hand, sleep-related breathing disorders lead to an increase in mean arterial pressure, but not pulse pressure [29].

Only three highly trained specialists measured the arterial properties in four different arterial territories by means of an ultrasound technique, which in experienced hands has high intraobserver and interobserver reproducibility within and across sessions [21,30]. We implemented a quality control programme to minimize measurement error in the blood pressure readings, which more readily occurs in obese individuals with a large arm circumference [8]. Our representative population sample was large enough to allow stratification for sex and had a wide age range. Sensitivity analyses, which accounted for antihypertensive drug treatment, serum cholesterol and blood glucose or the use of oral contraceptives or hormonal replacement therapy, were confirmatory. In comparison with two previous key reports with a similar focus [5,6], our study adds new information, because it had a substantially larger sample size allowing us to analyse men and women separately. In comparison to the study by Wildman *et al.* [6], we studied three additional arterial territories and we analysed the interaction between age and BMI without dichotomization of the distributions.

We demonstrated that already from a young age onwards, the diameter of large arteries and the stiffness of muscular arteries increases with higher BMI. In elastic arteries, the relationship between arterial stiffness and BMI seems to be modulated by sex and age. The mechanisms underlying the apparent differences in the associations of BMI with the properties of vascular as compared with elastic arteries need further clarification. Because among youth obesity is becoming a global problem, and because increased vascular stiffness is a forerunner of cardiovascular complications, our findings highlight the potential for prevention at a young age. Preliminary evidence from a small intervention study [31] suggested that in young adults weight loss augments carotid distensibility probably because of the decrease in blood pressure, but the generalizability of this conclusion to any type of artery remains to be proved, especially in children and adolescents.

Acknowledgements

The Flemish population study would not have been possible without the collaboration of the family physicians of the participants. The municipality Hechtel-Eksel (Belgium) gave logistic support. H. Celis T. Kuznetsova, Yan Li, and Ji-Guang Wang helped cleaning the database. The authors acknowledge the expert assistance of R. Bollen, S. Covens, L. Gijsbers, M.J. Jehoul, H. Truyens, S. Van Hulle, and R. Wolfs (Study Coordinating Centre, Leuven, Belgium).

References

1 World Health Organization. The problem of overweight and obesity. In: *Obesity: preventing and managing the global epidemic. Report of a WHO Consultation.* Geneva, Switzerland: World Health Organization; 1997. pp. 5–37.
2 Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999–2000. *JAMA* 2002; **288**:1723–1727.
3 Jelic S, Bartels MN, Mateika JH, Ngai P, DeMeersman RE, Basner RC. Arterial stiffness increases during obstructive sleep apneas. *Sleep* 2002; **25**:850–855.
4 Hall JE. The kidney, hypertension, and obesity. *Hypertension* 2003; **41**:625–633.
5 Ferreira I, Twisk JWR, van Mechelen W, Kemper HCG, Seidell JC, Stehouwer CDA. Current and adolescent body fatness and fat distribution: relationship with carotid intima-media thickness and large artery stiffness at the age of 36 years. *J Hypertens* 2004; **22**:145–155.
6 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.
7 Balkestein EJ, Staessen JA, Wang JG, van der Heijden-Spek JJ, Van Bortel L, Barlassina C, *et al.* Carotid and femoral artery stiffness in relation to three candidate genes in a white population. *Hypertension* 2001; **38**:1190–1197.
8 Kuznetsova T, Staessen JA, Kawecka-Jaszcz K, Babeanu S, Casiglia E, Filipovský J, *et al.* Quality control of the blood pressure phenotype in the European Project on Genes in Hypertension. *Blood Press Monit* 2002; **7**:215–224.
9 Van Bortel LM, Balkestein EJ, van der Heijden-Spek JJ, Vanmolkot FH, Staessen JA, Kragten JA, *et al.* Non-invasive assessment of local arterial pulse pressure: comparison of applanation tonometry and echo-tracking. *J Hypertens* 2001; **19**:1037–1044.
10 Hoeks APG, Reneman RS. Biophysical principles of vascular diagnosis. *J Clin Ultrasound* 1995; **23**:71–79.
11 Oren S, Grossman E, Frohlich ED. Arterial and venous compliance in obese and nonobese subjects. *Am J Cardiol* 1996; **77**:665–667.
12 Ardilouze JL, Fielding BA, Currie JM, Frayn KN, Karpe F. Nitric oxide and β-adrenergic stimulation are major regulators of preprandial and postprandial subcutaneous adipose tissue blood flow in humans. *Circulation* 2004; **109**:47–52.
13 Singhal A, Farooqi IS, Cole TJ, O'Rahilly S, Fewtrell M, Kattenhorn M, *et al.* Influence of leptin on arterial distensibility. A novel link between obesity and cardiovascular disease? *Circulation* 2002; **106**:1919–1924.
14 Verlohren S, Dubrovska G, Tsang SY, Essin K, Luft FC, Huang Y, *et al.* Visceral periadventitial adipose tissue regulates arterial tone of mesenteric arteries. *Hypertension* 2004; **44**:271–276.
15 Tounian P, Aggoun Y, Dubern B, Varille V, Guy-Grand B, Sidi D, *et al.* Presence of increased stiffness of the common carotid artery and endothelial dysfunction in severely obese children. *Lancet* 2001; **358**:1400–1404.
16 Danias PG, Tritos NA, Stuber M, Botnar RM, Kissinger KV, Manning WJ. Comparison of aortic elasticity determined by cardiovascular magnetic resonance imaging in obese versus lean adults. *Am J Cardiol* 2003; **91**:195–199.
17 Giltay EJ, Lambert J, Elbers JMH, Gooren LJG, Asscheman H, Stehouwer CDA. Arterial compliance and distensibility are modulated by body composition in both men and women but by insulin sensitivity only in women. *Diabetologia* 1999; **42**:214–221.

18 Sutton-Tyrrell K, Newman A, Simonsick EM, Havlik R, Pahor M, Lakatta E, *et al.* Aortic stiffness is associated with visceral adiposity in older adults enrolled in the Study of Health, Aging, and Body Composition. *Hypertension* 2001; **38**:429–433.

19 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.

20 Mangoni AA, Giannattasio C, Brunani A, Failla M, Colombo M, Bolla G, *et al.* Radial artery compliance in young, obese, normotensive subjects. *Hypertension* 1995; **26**:984–988.

21 Spek JJ, Hoeks APG, Struijker-Boudier HAJ, Van Bortel LMAB. Differences in vessel wall properties of large arteries between obese and lean subjects. *Nier und Hochdrukkrankheiten* 1995; **8**:431–432.

22 Westerbacka J, Vehkavaara S, Bergholm R, Wilkinson I, Yki-Järvinen H. Marked resistance of the ability of insulin decrease arterial stiffness characterizes human obesity. *Diabetes* 1999; **48**:821–827.

23 Oren A, Vos LE, Uiterwaal CSPM, Grobbee DE, Bots ML. Aortic stiffness and carotid intima-media thickness: two independent markers of subclinical vascular damage in young adults? *Eur J Clin Invest* 2003; **33**:949–954.

24 Mitchell GF, Parise H, Benjamin EJ, Larson MG, Keyes MJ, Vita JA, *et al.* Changes in arterial stiffness and wave reflection with advancing age in healthy men and women. The Framingham Heart Study. *Hypertension* 2004; **43**:1239–1245.

25 Hegazi RA, Sutton-Tyrrell K, Evans RW, Kuller LH, Belle S, Yamamoto M, *et al.* Relationship of adiposity to subclinical atherosclerosis in obese patients with type 2 diabetes. *Obes Res* 2003; **11**:1597–1605.

26 Nakanishi N, Suzuki K, Tatara K. Clustered features of the metabolic syndrome and the risk for increased aortic pulse wave velocity in middle-aged Japanese men. *Angiology* 2003; **54**:551–559.

27 Diamantopoulos EJ, Andreadis EA, Vassilopoulos CV, Vlachonikolis IG, Tarassi KE, Chatzis NA, *et al.* Association of specific HLA phenotypes with left ventricular mass and carotid intima-media thickness in hypertensives. *Am J Hypertens* 2001; **14**:632–636.

28 Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea. A population health perspective. *Am J Respir Crit Care Med* 2002; **165**:1217–1239.

29 Grote L, Hedner J, Peter JH. Mean blood pressure, pulse pressure and grade of hypertension in untreated hypertensive patients with sleep-related disorder. *J Hypertens* 2001; **19**:683–690.

30 Kool MJF, Van Merode T, Reneman RS, Hoeks APG, Struijker Boudier HAJ, Van Bortel LMAB. Evaluation of the reproducibility of a vessel wall movement detector system for assessment of large artery properties. *Cardiovasc Res* 1994; **28**:610–614.

31 Balkestein EJ, van Aggel-Leijssen DP, van Baak MA, Struijker-Boudier HA, Van Bortel LM. The effect of weight loss with or without exercise training on large artery compliance in healthy obese men. *J Hypertens* 1999; **17**:1831–1835.