Regional body composition as a determinant of arterial stiffness in the elderly: The Hoorn Study

Marieke B. Snijder[a,e], Ronald M.A. Henry[a], Marjolein Visser[a,e], Jacqueline M. Dekker[a], Jacob C. Seidell[a,e], Isabel Ferreira[a], Lex M. Bouter[a], John S. Yudkin[a,d,f], Nico Westerhof[b,d] and Coen D.A. Stehouwer[a,c,d]

Objective **To estimate the relation of precisely measured regional body composition with peripheral and central arterial stiffness in the elderly.**

Methods **We investigated 648 participants (mean age 69.0 ± 6.0 years) of the Hoorn Study, a population-based cohort study. Trunk fat, leg fat, trunk lean and leg lean mass were distinguished by dual-energy X-ray absorptiometry. We used ultrasound to measure the distensibility and compliance of the carotid, femoral and brachial arteries, and carotid Young's elastic modulus, as estimates of peripheral stiffness. As estimates of central stiffness we measured carotid–femoral transit time, aortic augmentation index and systemic arterial compliance.**

Results **After adjustment for sex, age, height, mean arterial pressure, leg lean and leg fat mass, a larger trunk fat mass was consistently associated with higher peripheral arterial stiffness (standardized beta (β) of mean Z-scores of all three large arteries −0.24, $P < 0.001$). In contrast, larger leg fat mass (β = 0.15, $P = 0.009$) and leg lean mass (β = 0.09, $P = 0.20$) were associated with lower peripheral arterial stiffness. Trunk or leg fat mass were not associated with central arterial stiffness. Leg lean mass, however, was consistently associated with lower central arterial stiffness (β = 0.29, $P < 0.001$).**

Conclusions **Trunk fat mass may have adverse effects on peripheral, but not on central arterial stiffness, while leg fat was not harmful and may have a slight protective effect. Larger leg lean mass was the most important determinant of lower central arterial stiffness. These results provide a pathophysiological framework to explain not only the higher cardiovascular risk in individuals with larger trunk fat mass, but also the reduced cardiovascular risk in individuals with larger leg lean and fat mass. *J Hypertens* 22:2339–2347 © 2004 Lippincott Williams & Wilkins.**

Journal of Hypertension 2004, **22**:2339–2347

Keywords: arterial stiffness, body composition, fat distribution, muscle, elderly

[a]Institute for Research in Extramural Medicine, [b]Department of Physiology, [c]Department of Internal Medicine and [d]Institute for Cardiovascular Research, VU University Medical Center, Amsterdam, [e]Institute of Health Sciences, Faculty of Earth and Life Sciences, Vrije Universiteit, Amsterdam, The Netherlands and [f]Department of Medicine, Diabetes and Cardiovascular Disease Academic Unit, University College London Medical School, London, UK.

Sponsorship: This study was supported financially by The Netherlands Heart Foundation (grant No 98.154).

Correspondence and requests for reprints to Ms Marieke B. Snijder, Institute for Research in Extramural Medicine, VU University Medical Center, Van der Boechorststraat 7, 1081 BT Amsterdam, The Netherlands.
Tel: +31 20 4446942; fax: +31 20 4446940; e-mail: marieke.snijder@falw.vu.nl

Received 23 March 2004 **Revised**19 July 2004
Accepted 28 July 2004

Introduction

Obesity, and in particular abdominal fat accumulation, is an independent risk factor for cardiovascular disease [1,2]. In contrast, peripheral fat and muscle may independently contribute to a *lower* risk for cardiovascular disease [3–9]. The mechanisms underlying these contrasting associations are not completely understood.

Increased arterial stiffness may represent a pathway through which obesity may lead to cardiovascular disease. Arterial stiffening impairs the ability of the arterial system to handle the pressure boost at systole, which leads to increased systolic blood pressure, decreased diastolic blood pressure, increased left ventricular mass, and decreased diastolic coronary perfusion [10]. Arterial stiffness is known to increase with ageing, hypertension and with deteriorating glucose tolerance status. Nevertheless, arterial stiffness is not uniform along the arterial tree, and depends on the type of artery (e.g. elastic versus muscular). The response to ageing and other risk factors is also different along the arterial tree [11–15].

Several studies have considered obesity or fat distribution as determinants of arterial stiffness [16–24]. The results, however, have been inconsistent, which may be due to the limited number of subjects [16–19,21,24], or because stiffness has been estimated in only one specific artery [16,18–21,23,24]. In addition, usually only anthropometric measures [16,18,22,24] or bio-impedance [20] have been used to assess obesity or body composition, which are relatively inaccurate methods, in particular in obese and elderly individuals [25–27].

0263-6352

We hypothesized that abdominal fat may be associated with higher arterial stiffness, and that, in contrast, peripheral fat and lean mass may be associated with lower arterial stiffness. To systematically investigate this, we examined data of a large, population-based study. Body composition was estimated by dual-energy X-ray absorptiometry (DXA), which enables the distinction of central and peripheral fat and lean mass [9]. Arterial stiffness was estimated from the distensibility and compliance of three large (carotid, femoral and brachial) arteries (as estimates of peripheral arterial stiffness), as well as from carotid–femoral transit time, aortic augmentation index and systemic arterial compliance (as estimates of central arterial stiffness).

Methods

Subjects

The Hoorn Study is a population-based cohort study of glucose metabolism and its complications, which started in 1989 [28]. It consisted of 2484 men and women aged 50–75 years at baseline. In 2000–2001, a third examination was carried out among surviving participants who gave their permission to be re-contacted. We invited all participants who had diabetes, as determined by a 75-g oral glucose tolerance test (OGTT) or by diabetes treatment ($n = 176$), at the second examination of the entire cohort in 1996–1998 [29]. We also invited a random sample of participants who had normal glucose tolerance ($n = 705$) or impaired glucose tolerance ($n = 193$) in 1996–1998. Of 1074 individuals invited, 648 (60.3%) persons participated. The main reasons for not participating in the 2000–2001 follow-up examination were lack of interest (30%) or co-morbidity (23%). Other reasons were high age (7%), unwillingness to travel (6%), participation considered too time-consuming (6%), and miscellaneous reasons (15%), while 13% gave no reason. For the present study cross-sectional data of this examination were analysed. The Ethical Review Committee of the VU University Medical Center approved the study protocol and all participants gave their written informed consent.

Body composition

Total body fat percent, and fat and lean soft-tissue mass of the trunk and legs were determined by whole-body dual-energy X-ray absorptiometry (DXA) (QDR-2000, software version 7.20D; Hologic, Brussels, Belgium), as previously described [9]. All DXA scans were performed and read by one investigator.

Peripheral arterial stiffness

The methods of obtaining peripheral arterial stiffness measures within the Hoorn Study have been described before [12]. Briefly, we obtained the diameter (D) and distension (ΔD) of the right common carotid, the right common femoral and the right brachial arteries, and the intima–media thickness (IMT) of the right carotid artery by ultrasound. Brachial systolic and diastolic pressures were assessed in the left upper arm. Brachial pulse pressure (PP) and brachial mean arterial pressure (MAP) were calculated. PP at the carotid and femoral arteries was calculated by the distension waveform calibration method, which is more accurate than using brachial PP [30,31]. All ultrasound measurements were performed by a single sonographer.

Distensibility (DC) and compliance (CC) coefficients were calculated from D, ΔD and PP [32]. Distensibility reflects the elastic properties of an artery, whereas the compliance reflects the buffering capacity of the artery. From carotid IMT, D and DC, we calculated Young's elastic modulus (E), an estimate of the intrinsic elastic properties of the vessel wall.

Central arterial stiffness

The carotid–femoral transit time (TT) is the travelling time of a pressure wave from the common carotid to the femoral artery, a measure of the aortic (thoracic–abdominal) compliance. It is closely related to the carotid–femoral pulse wave velocity [33,34], as measured by the length of the carotid–femoral arterial segment divided by carotid–femoral TT. However, as non-invasive measurement of this length may introduce error, in particular in obese [32] and older patients [34], we chose to use the carotid–femoral TT, and adjust for height in the statistical analyses. We determined the carotid–femoral TT by continuous measurement of the diameter (distension curves) of the right carotid artery and the right femoral artery [12]. We then determined the average time delay (mean of three recordings of 4 s/artery) from the ECG trigger to 10% of the ascending slope of the distension curve and subtracted the carotid value from the femoral value to obtain the femoral–carotid TT [35].

Radial applanation tonometry was used to obtain the aortic augmentation index (AI), and was performed with a piezo-resistive pressure transducer (Millar SPT-301; Millar Instruments Inc., Houston, Texas, USA) connected to an arterial waveform analysis device (Sphygmocor; AtCor Medical Ltd., Moreton-in-Marsh, UK). The AI represents the extra pressure boost with which the left ventricle must cope due to (early) wave reflection. The AI was calculated as augmented pressure divided by (tonometrically derived) central pulse pressure.

Systemic arterial compliance reflects the overall buffering capacity of the arterial system, but mainly of the proximal aorta [33,36]. Systemic arterial compliance (SAC) in ml/mmHg was determined according to two methods. The first method (SAC1) was the time-decay method based on the Windkessel model [37] and used data obtained by applanation tonometry (see above).

The second method used the ratio of stroke volume to aortic pulse pressure to estimate systemic arterial compliance (SAC2) [38]. Here we chose to estimate the aortic pulse pressure by calibration of carotid pulse pressure [12], because studies have suggested that this may be the most accurate estimate [31,39,40], and data on this estimate were available for a larger number of persons in our study. Stroke volume was calculated as the ratio of cardiac output and heart rate. Cardiac output (ml/s) was measured by pulse wave Doppler echocardiography (3.5 MHz transducer, HP 5500; Massachusetts, USA) of the left ventricular outflow tract. All measurements were performed by one investigator.

Additional measurements

We determined fasting glucose, insulin, post-load glucose after a 75-g OGTT, high-density (HDL) and low-density (LDL) lipoprotein cholesterol, triglycerides, serum creatinine, body mass index (BMI), waist circumference, and prior cardiovascular disease, as described elsewhere [9,41,42]. We obtained self-reported information on health status, medical history, current medication use, physical activity (min/week), alcohol intake (g/day), macronutrient intake (energy %) and current smoking (yes/no) by questionnaires.

Statistical methods

Multiple linear regression analyses were performed to investigate the association between body composition (determinants) and estimates of arterial stiffness (outcomes). First we considered trunk fat, trunk lean, leg fat and leg lean mass together as central determinants of peripheral and central arterial stiffness, adjusted for age, gender, height and MAP. In a second model we additionally adjusted for glucose tolerance status. Next, we adjusted for other potential confounders by adding these variables to the regression models. Effect modification by gender was tested by adding product terms to the models. Effect modification was considered statistically significant if $P < 0.05$. We considered the stability of the regression models to be disturbed by multi-colinearity if the tolerance was < 0.1. Standardized betas are reported. A standardized beta of 0.1 indicates that when the independent variable increases by 1 SD, the dependent variable increases by 0.1 SD.

A summarizing peripheral stiffness variable was constructed by means of *Z*-scores. We calculated (sex-specific) *Z*-scores for each peripheral stiffness measure (DC, CC and E) of each artery, and multiplied the *Z*-score of E by −1. A *Z*-score is calculated as the individual value minus the mean value in the study population, divided by the standard deviation. We then performed regression analyses using the mean of the seven *Z*-scores as dependent variable. Similarly, we constructed a summarizing score for central stiffness measures (AI, SAC1 and SAC2). The *Z*-scores were multiplied by −1, except for AI. Because carotid–femoral TT was available in fewer persons, we did not include this measure in the mean *Z*-score for central arterial stiffness. All statistical analyses were performed using SPSS for Windows (version 10.1.0; Chicago, Illinois, USA).

Results

Table 1 shows characteristics of the study population. Of the 648 participants, 25 persons were excluded because of missing DXA data. Another 139 participants did not take part in the ultrasound examination and were also excluded from all analyses. The main reason for missing ultrasound data was poor definition of the arterial wall due to obesity; other reasons were logistical and technical.

Table 2 shows estimates of peripheral and central arterial stiffness of the study population. Data on central arterial stiffness were mainly missing due to device availability. Nevertheless, subjects with missing data were statistically significantly older, had higher BMI and total fat percentage, and were more likely to have diabetes (data not shown).

Associations of body composition with peripheral arterial stiffness

After adjustment for the other body composition variables, trunk fat mass was consistently associated with larger arterial stiffness as estimated from DC, CC and E (Model 1, Table 3). Addition of trunk lean mass to this model did not change the results of the other variables, and because of the strong correlation between trunk lean and leg lean mass (Pearson's $r = 0.93$), the model including trunk lean mass became disturbed by multi-colinearity. Therefore, Model 1 is shown without adjustment for trunk lean mass. In contrast to trunk fat mass, larger leg fat mass was associated with lower femoral stiffness. Larger leg lean mass was also associated with higher compliance in the femoral and brachial arteries. Associations with fat mass were generally stronger in men than in women, and associations with lean mass were stronger in women, but there was no statistically significant effect modification by gender, except for the association between leg fat mass and carotid E (P interaction $= 0.03$). The independent associations of trunk fat, leg fat and leg lean mass with peripheral arterial stiffness are further summarized and illustrated in Figures 1 and 2. We performed regression analyses using the mean of the seven *Z*-scores as dependent variable (similar to models in Table 3) and plotted the standardized betas in Figure 1. In Figure 2 we show the results for each peripheral artery separately.

Additional adjustment of Model 1 for lifestyle (physical activity, smoking, alcohol or nutrient intake), compo-

Table 1 Characteristics of the study population

	Men ($n = 244$)	Women ($n = 240$)	P
Age (years)	69.1 ± 5.9	69.0 ± 6.3	0.98
Anthropometry			
Height (cm)	175.9 ± 6.1	163.5 ± 6.4	< 0.01
Weight (kg)	82.1 ± 10.1	70.4 ± 9.7	< 0.01
BMI (kg/m^2)	26.5 ± 3.0	26.3 ± 3.2	0.48
Waist circumference (cm)	97.6 ± 9.1	87.9 ± 10.0	< 0.01
DXA			
Total body fat percent (%)	27.5 ± 5.9	40.0 ± 6.1	< 0.01
Total fat mass (kg)	22.5 ± 6.7	28.2 ± 7.4	< 0.01
Total lean mass (kg)	55.3 ± 5.8	39.2 ± 4.5	< 0.01
Trunk fat mass (kg)	12.2 ± 4.6	13.4 ± 4.7	< 0.01
Trunk lean mass (kg)	27.9 ± 2.8	20.1 ± 2.3	< 0.01
Leg fat mass (kg)	6.3 ± 1.8	9.9 ± 2.8	< 0.01
Leg lean mass (kg)	17.5 ± 2.3	12.4 ± 1.8	< 0.01
Metabolic variables			
Systolic blood pressure (mmHg)	138.9 ± 16.6	142.6 ± 21.1	0.03
Diastolic blood pressure (mmHg)	77.1 ± 8.2	74.9 ± 9.3	< 0.01
Pulse pressure (mmHg)	61.8 ± 12.4	67.7 ± 16.3	< 0.01
Mean arterial pressure (mmHg)	97.7 ± 10.2	97.5 ± 12.1	0.84
Hypertension (%)	64.3	65.3	0.83
LDL-cholesterol (mmol/l)	3.50 ± 0.85	3.87 ± 0.92	< 0.01
HDL-cholesterol (mmol/l)	1.26 ± 0.31	1.62 ± 0.43	< 0.01
Triglycerides (mmol/l)	1.3 (1.0–1.7)	1.2 (0.9–1.7)	0.40
Fasting glucose (mmol/l)	6.15 ± 1.21	6.09 ± 1.44	0.64
Post-load glucose (mmol/l)[a]	6.92 ± 2.59	7.14 ± 2.46	0.36
Fasting insulin (pmol/l)	57.0 (40.3–75.0)	53.0 (39.0–79.5)	0.76
Glycated haemoglobin (%)	5.91 ± 0.72	6.01 ± 0.67	0.15
IGM (%)	28.8	24.5	0.28
DM (%)	22.2	21.9	0.94
Prior cardiovascular disease (%)	44.3	44.0	0.95
(Micro-) albuminuria (%)	16.8	8.8	< 0.01
Serum creatinine (μmol/l)	130.3 ± 17.1	86.8 ± 9.4	< 0.01
Lifestyle			
Current smokers (% yes)	18.0	12.5	0.09
Physical activity (min/week)	1110 (609–1300)	1328 (840–2040)	0.02
Alcohol drinker (%)	97.9	91.5	< 0.01
Alcohol intake (g/day)	12.7 (3.7–28.7)	4.2 (0.7–12.8)	< 0.01
Fat intake (% energy intake)	35.2 ± 5.6	34.0 ± 5.7	0.03
Carbohydrate intake (% energy intake)	44.1 ± 6.3	46.6 ± 6.5	< 0.01

Data are presented as mean ± SD, percentage, or median (interquartile range). BMI, body mass index; DXA, dual-energy X-ray absorptiometry; LDL, low-density lipoprotein; HDL, high-density lipoprotein; IGM, impaired glucose metabolism; DM, diabetes mellitus. [a]Post load glucose was determined in 216 men and 211 women.

nents of the metabolic syndrome (LDL- and HDL-cholesterol, triglycerides, hypertension), and other cardiovascular risk factors (serum creatinine, (micro-) albuminuria and prior cardiovascular disease) did not materially change the associations (data not shown). Adjustment for HbA_{1c}, insulin, fasting or post-load glucose attenuated the associations, in particular in the femoral and brachial arteries (data not shown). After adjustment for insulin and fasting and post-load glucose levels together, all associations weakened and most became non-significant, except for the associations with carotid E, and femoral CC (data not shown). Model 2 shows the independent associations of trunk fat, leg fat and leg lean mass with peripheral stiffness after adjustment for glucose tolerance status.

Table 4 provides insight into which elements of the peripheral arterial stiffness estimates (i.e. D, ΔD, PP or IMT) contributed to the associations shown in Table 3. The associations were mainly determined by D or ΔD, or by both in the femoral artery, but not by PP.

There was no statistically significant effect modification by gender. None of the regression models were disturbed by multi-colinearity.

Associations of body composition with central arterial stiffness

Trunk fat mass was not associated with higher central arterial stiffness, except for SAC2 (Table 5). Leg lean mass was consistently associated with lesser central arterial stiffness. There was no statistically significant effect modification by gender. The independent associations of trunk fat, leg fat and leg lean mass with central arterial stiffness are further illustrated in Figure 3, with the mean Z-scores of each central stiffness estimate as dependent variables. Because carotid–femoral TT was available in fewer persons (see Table

Table 2 Estimates of peripheral and central arterial stiffness

	Men	Women	*P*
Peripheral arterial stiffness[a]			
Carotid artery			
Distensibility coefficient (10^{-3}/kPa)	12.30 ± 4.47	11.42 ± 4.55	0.03
Compliance coefficient (mm2/kPa)	0.65 ± 0.25	0.48 ± 0.18	< 0.01
Young's elastic modulus (kPa)	0.92 ± 0.49	0.98 ± 0.57	0.28
Distension (μm)	373 ± 123	331 ± 92	< 0.01
Diameter (mm)	8.35 ± 1.10	7.48 ± 0.97	< 0.01
Pulse pressure (mmHg)	58.7 ± 13.3	65.1 ± 17.9	< 0.01
Intima–media thickness (mm)	0.88 ± 0.18	0.83 ± 0.15	< 0.01
Femoral artery			
Distensibility coefficient (10^{-3}/kPa)	4.67 ± 2.08	4.86 ± 2.22	0.32
Compliance coefficient (mm^2/kPa)	0.42 ± 0.21	0.35 ± 0.18	< 0.01
Distension (μm)	207 ± 75	209 ± 74	0.78
Diameter (mm)	10.76 ± 1.87	9.51 ± 1.24	< 0.01
Pulse pressure (mmHg)	66.6 ± 14.0	74.3 ± 20.4	< 0.01
Brachial artery			
Distensibility coefficient (10^{-3}/kPa)	7.73 ± 3.89	8.09 ± 4.50	0.35
Compliance coefficient (mm^2/kPa)	0.15 ± 0.07	0.11 ± 0.06	< 0.01
Distension (μm)	152 ± 69	142 ± 66	0.10
Diameter (mm)	5.04 ± 0.62	4.23 ± 0.59	< 0.01
Pulse pressure (mmHg)	61.8 ± 12.4	67.7 ± 16.3	< 0.01
Central arterial stiffness			
Carotid–femoral transit time (ms)[b]	55.8 ± 16.8	52.0 ± 16.1	0.08
Aortic augmentation index (%)[c]	144.9 ± 19.1	156.5 ± 18.5	< 0.01
Systemic arterial compliance (ml/mmHg)[d]	0.83 ± 0.33	0.64 ± 0.25	< 0.01
Systemic arterial compliance (ml/mmHg)[e]	1.19 ± 0.34	0.93 ± 0.30	< 0.01

Data are presented as mean ± SD. [a]244 men and 240 women.[b]114 men and 121 women. [c]272 men and 270 women. [d]238 men and 253 women, estimated by time-decay method. [e]229 men and 245 women, estimated by stroke volume-to-pulse pressure ratio.

Table 3 Associations (standardized betas) of body composition by DXA with peripheral arterial stiffness estimates

		Carotid artery			Femoral artery		Brachial artery	
		DC	CC	E	DC	CC	DC	CC
Model 1	Trunk fat mass	−0.15**	−0.08*	0.15**	−0.18**	−0.26**	−0.14**	−0.16**
	Leg fat mass	0.07	0.04	−0.08	0.13**	0.22**	0.05	0.08
	Leg lean mass	−0.07	0.00	0.00	0.09	0.36**	−0.06	0.14*
Model 2[a]	Trunk fat mass	−0.13**	−0.07	0.14**	−0.02	−0.13**	−0.05	−0.09
	Leg fat mass	0.04	0.02	−0.07	0.02	0.13**	−0.02	0.04
	Leg lean mass	−0.08	−0.01	0.01	0.03	0.31**	−0.09	0.12

All models are adjusted for age, height, sex, mean arterial pressure and the other two body composition variables. ** $P < 0.05$; * $P < 0.10$. DXA, dual-energy X-ray absorptiometry; DC, distensibility coefficient; CC, compliance coefficient; E, Young's elastic modulus. [a]Model 2 is Model 1 with additional adjustment for glucose tolerance status.

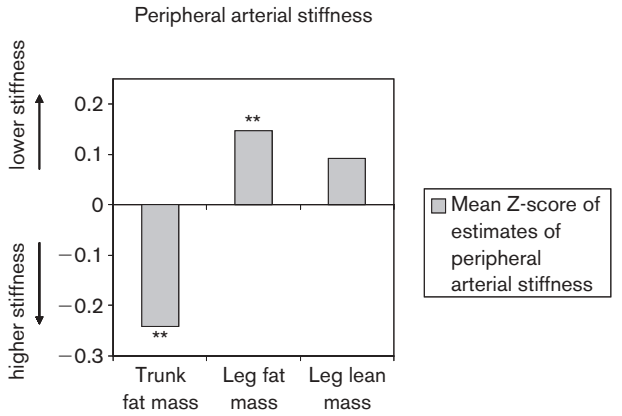
2), we did not include this measure in the mean *Z*-score presented in Figure 3. Results including this measure yielded similar results (data not shown).

Additional adjustment for heart rate did not influence the association between body composition and carotid–femoral TT (data not shown). Adjustment for lifestyle measures did not affect any of the associations, nor did adjustment for components of the metabolic syndrome (LDL- and HDL-cholesterol, fasting and post-load glucose, ln-transformed insulin, triglycerides, hypertension) and other cardiovascular risk factors (serum creatinine, (micro-) albuminuria, and prior cardiovascular disease). Model 2 shows the association adjusted for glucose tolerance status. None of the regression models were disturbed by multi-colinearity.

Discussion

This study, in men and women aged 60–86 years, had three major findings. First, larger trunk fat mass was associated with higher peripheral, but not central, arterial stiffness. Secondly, and in contrast, larger leg fat mass was not associated with higher peripheral arterial stiffness, but was instead associated with *lower*

Fig. 1



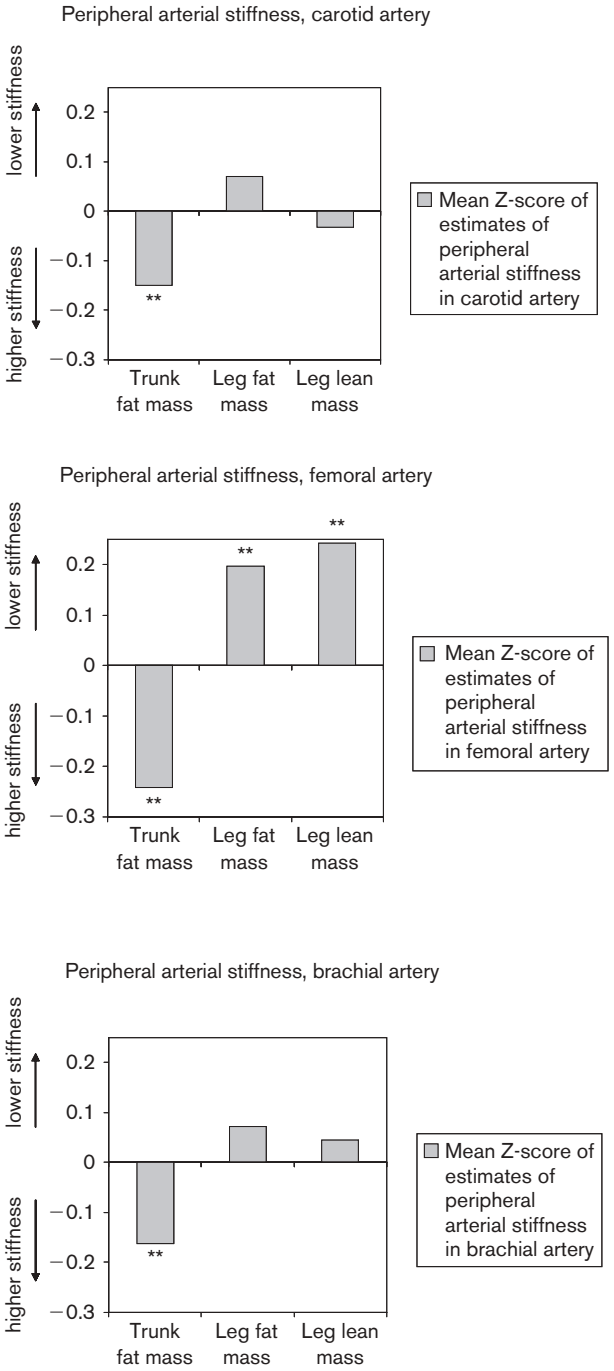
Independent associations (standardized betas,) of body composition variables, adjusted for each other, age, height, sex and mean arterial pressure, with the mean Z-scores of all measures for peripheral arterial stiffness†. ** $P < 0.01$. († Distensibility and compliance of the carotid, femoral and brachial arteries and carotid Young's elastic modulus.)

peripheral arterial stiffness, notably of the femoral artery. Thirdly, larger leg lean mass was consistently, and independently of trunk and leg fat mass, strongly associated with lower central and less femoral and brachial arterial stiffness. These results provide a pathophysiological framework for understanding how abdominal obesity may contribute to cardiovascular disease, and how leg fat and lean mass may protect against cardiovascular disease.

Results of previous studies on body composition and arterial stiffness have not shown consistent results. Most studies were performed with a relatively small number of individuals (24–75) [16–19,21,24] and some were restricted to children [20,21] or men only [16]. In some studies measures of obesity (usually BMI) were associated with higher arterial stiffness [16,19–23], while other studies found the opposite [17,18,24]. The present study has important advantages, because it was large and population-based, and because comprehensive measures of both peripheral and central arterial stiffness were determined, as well as a very accurate and precise measurement of body composition. The latter is important because a higher BMI represents larger fat as well as larger lean mass [9]. Because trunk fat mass and leg (or trunk) lean mass have opposite associations with arterial stiffness, the association of BMI with arterial stiffness will depend on the extent to which BMI reflects fat versus lean mass, and this may explain the divergent results reported in previous studies.

Larger trunk fat mass was associated with higher peripheral arterial stiffness in the elastic carotid artery and the muscular femoral and brachial arteries. Adjustment for glucose tolerance status did not materially affect the associations with carotid artery stiffness, but decreased those with femoral and brachial artery stiffness (Table 3). This finding may indicate that the

Fig. 2



Independent associations (standardized betas, β) of body composition variables, adjusted for each other, age, height, sex and mean arterial pressure, with the mean Z-scores of measures for peripheral arterial stiffness† in each artery separately. ** $P < 0.01$. († Distensibility and compliance of the carotid, femoral and brachial arteries and carotid Young's elastic modulus.)

Table 4 Associations (standardized betas) of body composition measured by DXA with individual elements of the peripheral arterial stiffness estimates

		Carotid artery				Femoral artery			Brachial artery		
		D	ΔD	PP	IMT	D	ΔD	PP	D	ΔD	PP
Model 1	Trunk fat mass	0.12**	−0.07	0.06	0.02	−0.17**	−0.24**	0.04	−0.02	−0.13**	0.06
	Leg fat mass	−0.04	0.00	−0.05	−0.01	0.17**	0.23**	−0.03	0.09*	0.05	−0.03
	Leg lean mass	0.12	−0.01	0.01	0.13	0.41**	0.32**	−0.01	0.36**	0.03	−0.07
Model 2[a]	Trunk fat mass	0.12**	−0.07	0.03	−0.04	−0.17**	−0.05	0.04	−0.05	−0.05	0.03
	Leg fat mass	−0.04	−0.01	−0.02	0.04	0.17**	0.11*	−0.02	0.13**	0.01	−0.00
	Leg lean mass	0.10	−0.02	0.01	0.14	0.41**	0.25**	−0.01	0.37**	−0.00	−0.07

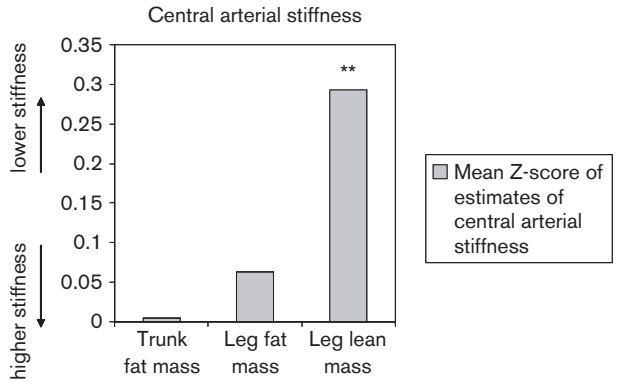
All models are adjusted for age, height, sex, mean arterial pressure and the other two body composition variables. ** $P < 0.05$, * $P < 0.10$. DXA, dual-energy X-ray absorptiometry; D, diameter; ΔD, distension; PP, pulse pressure; IMT, intima–media thickness. [a]Model 2 is Model 1 with additional adjustment for glucose tolerance status.

Table 5 Associations (standardized betas) of body composition by DXA with central arterial stiffness estimates

		Car-fem TT	AI	SAC1	SAC2
Model 1	Trunk fat mass	0.06	−0.06	0.05	−0.08*
	Leg fat mass	0.14	−0.06	0.08	0.09*
	Leg lean mass	0.23**	−0.15**	0.17**	0.30**
Model 2[a]	Trunk fat mass	0.10	−0.08	0.06	−0.03
	Leg fat mass	0.12	−0.05	0.07	0.05
	Leg lean mass	0.21*	−0.15**	0.17**	0.29**

All models are adjusted for age, height, sex, mean arterial pressure and the other two body composition variables. ** $P < 0.05$; * $P < 0.10$. DXA, dual-energy X-ray absorptiometry; Car–fem TT, carotid–femoral transit time; AI, augmentation index; SAC1, systemic arterial compliance by time-decay method; SAC2 systemic arterial compliance by stroke volume-to-pulse pressure ratio. [a]Model 2 is Model 1 with additional adjustment for glucose tolerance status.

Fig. 3



Independent associations (standardized betas, β) of body composition variables, adjusted for each other, age, height, sex and mean arterial pressure, with the mean Z-scores of measures for central arterial stiffness[†]. ** $P < 0.01$. ([†] Aortic augmentation index, systemic arterial compliance by time decay method and systemic arterial compliance by stroke volume-to-pulse pressure ratio.)

association of trunk fat with femoral and brachial artery stiffness is, in part, mediated by trunk-fat-induced glucose intolerance. However, we cannot exclude confounding, because our study population was a sample stratified for glucose tolerance status, and individuals who are glucose intolerant have more trunk fat, on average. Nevertheless, the concept that intra-abdominal fat in particular contributes to hyperglycaemia and hyperinsulinaemia, possibly due to an increased secretion of free fatty acids (FFA) [1], is generally accepted. Because DXA cannot distinguish between visceral and subcutaneous trunk fat, additional studies are needed to investigate the effect of subcutaneous fat, which is the largest component of trunk fat, versus visceral fat on peripheral arterial stiffness.

Several mechanisms can explain the relation between abdominal obesity and arterial stiffness. Both insulin and glucose levels attenuated some of the associations we found in the present study, which supports the concept that insulin and/or glucose levels may mediate the relations between body composition and peripheral arterial stiffness. Hyperinsulinaemia may promote endothelial dysfunction, oxidative stress, vascular smooth muscle cell growth, and stimulation of the sympathetic nervous system [43], all of which may contribute to arterial stiffness. Advanced glycation end-products can form cross-links in collagen fibres, thereby decreasing the distensibility of the arterial wall [44]. In addition, inflammatory markers may also be mediators of the

relationships observed. These markers are increased in obesity, and have been shown to relate to endothelial dysfunction [45,46]. Finally, several other proteins secreted by adipose tissue, such as resistin [47], adiponectin [48] and leptin [20,49], have been shown to be a possible link between obesity and vascular structure and function.

Our finding that storage of fat in the legs may be favourable for peripheral arterial stiffness provides a potential explanation for the inverse relationship between hip circumference and cardiovascular risk [3–6]. The underlying mechanisms linking leg fat to (lower) arterial stiffness remain to be identified. However, it is becoming increasingly clear that leg fat is metabolically different from trunk fat, and is associated with a more favourable metabolic profile [7–9]. Leg fat has greater lipolytic activity than fat in the abdominal region [50,51], thus being able to take up FFA efficiently from the circulation, thereby protecting against the development of hyperglycaemia and hyperinsulinaemia [9,52]. In addition, leg fat and trunk fat may differ in secretion of adipokines that influence vascular function and structure. There are some known differences in secretion of leptin, adiponectin and interleukin-6 between abdominal subcutaneous and visceral fat [53–56], but less is known about differences between abdominal and femoral subcutaneous adipose tissue. Taken together, we speculate that metabolic differences between leg and trunk fat may be responsible for their opposite associations with peripheral arterial stiffness. More work in this area is clearly needed.

We found that leg lean (or muscle) mass was a more important determinant of central arterial stiffness than was fat mass. As muscle mass increases, so will the requirements for blood supply, resulting in a higher cardiac output and stroke volume and size adaptation of the arteries. This is also demonstrated by the larger diameter and distension of both femoral and brachial arteries in people with more leg lean mass in our study.

The differences in the impact of body composition on the various arterial stiffness estimates suggests that, like the influence of ageing and other risk factors [11,14], the impact of body composition is not uniform along the arterial tree. Local differences in physiological or mechanical mechanisms (e.g. between proximal elastic versus peripheral muscular arteries) may play a role [11,14].

The present study has some limitations. First, because of the cross-sectional design of the study, we cannot exclude the possibility that the associations between fat distribution and arterial stiffness are caused by an unmeasured common underlying factor. However, adjustment for many alternative determinants, such as renal function, hypertension and lifestyle variables, did not change our findings. Prospective studies are needed to address this issue further. Secondly, because we investigated an older Caucasian population, it is unclear whether these results apply to younger subjects or other ethnic populations. Finally, because of selective mortality and loss of follow-up of the unhealthiest subjects (who are likely to have had increased fatness and increased arterial stiffness), we probably have investigated a relatively healthy population and therefore may have underestimated the true associations (healthy survivor effect).

We conclude that trunk fat has adverse effects on peripheral, but not central, arterial stiffness. These adverse effects are partly, but not completely, explained by hyperglycaemia and hyperinsulinaemia. In contrast, peripheral fat mass was not harmful and may possibly be slightly beneficial for peripheral arterial stiffness. In addition, larger lean mass was strongly associated with lower central arterial stiffness and lower peripheral stiffness in the muscular arteries. These results provide a pathophysiological framework to explain not only the higher cardiovascular risk in individuals with larger trunk fat mass, but also the reduced cardiovascular risk in individuals with larger leg lean and fat mass.

Acknowledgement

We thank Rosemarie van Eijck-Weel for her excellent technical assistance.

References

1 Bjorntorp P. Body fat distribution, insulin resistance, and metabolic diseases. *Nutrition* 1997; **13**:795–803.
2 Abate N, Garg A, Peshock RM, Stray-Gundersen J, Grundy SM. Relationships of generalized and regional adiposity to insulin sensitivity in men. *J Clin Invest* 1995; **96**:88–98.
3 Lissner L, Bjorkelund C, Heitmann BL, Seidell JC, Bengtsson C. Larger hip circumference independently predicts health and longevity in a Swedish female cohort. *Obes Res* 2001; **9**:644–646.
4 Seidell JC, Perusse L, Despres JP, Bouchard C. Waist and hip circumferences have independent and opposite effects on cardiovascular disease risk factors: the Quebec Family Study. *Am J Clin Nutr* 2001; **74**:315–321.
5 Snijder MB, Dekker JM, Visser M, Yudkin JS, Stehouwer CD, Bouter LM, *et al.* Larger thigh and hip circumferences are associated with better glucose tolerance: the Hoorn study. *Obes Res* 2003; **11**:104–111.
6 Snijder MB, Dekker JM, Visser M, Bouter LM, Stehouwer CD, Kostense PJ, *et al.* Associations of hip and thigh circumferences independent of waist circumference with the incidence of type 2 diabetes: the Hoorn Study. *Am J Clin Nutr* 2003; **77**:1192–1197.
7 Van Pelt RE, Evans EM, Schechtman KB, Ehsani AA, Kohrt WM. Contributions of total and regional fat mass to risk for cardiovascular disease in older women. *Am J Physiol Endocrinol Metab* 2002; **282**:E1023–1028.
8 Tanko LB, Bagger YZ, Alexandersen P, Larsen PJ, Christiansen C. Peripheral adiposity exhibits an independent dominant antiatherogenic effect in elderly women. *Circulation* 2003; **107**:1626–1631.
9 Snijder MB, Dekker JM, Visser M, Bouter LM, Stehouwer CD, Yudkin JS, *et al.* Trunk fat and leg fat have independent and opposite associations with fasting and postload glucose levels. The Hoorn Study. *Diabetes Care* 2004; **27**:372–377.
10 Westerhof N, O'Rourke MF. Haemodynamic basis for the development of left ventricular failure in systolic hypertension and for its logical therapy. *J Hypertens* 1995; **13**:943–952.

11 O'Rourke MF, Mancia G. Arterial stiffness. *J Hypertens* 1999; **17**:1–4.
12 Henry RM, Kostense PJ, Spijkerman AM, Dekker JM, Nijpels G, Heine RJ, *et al*. Arterial stiffness increases with deteriorating glucose tolerance status: the Hoorn Study. *Circulation* 2003; **107**:2089–2095.
13 Safar ME, Benetos A. Factors influencing arterial stiffness in systolic hypertension in the elderly: role of sodium and the renin–angiotensin system. *Am J Hypertens* 2003; **16**:249–258.
14 O'Rourke MF, Staessen JA, Vlachopoulos C, Duprez D, Plante GE. Clinical applications of arterial stiffness; definitions and reference values. *Am J Hypertens* 2002; **15**:426–444.
15 Schram MT, Henry RMA, van Dijk RAJM, Kostense PJ, Dekker JM, Nijpels G, *et al*. Increased central artery stiffness in impaired glucose metabolism and type 2 diabetes. The Hoorn Study. *Hypertension* 2004; **43**: 176–181.
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 JM, Gooren LJ, Asscheman H, Stehouwer CD. 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 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.
19 Resnick LM, Militianu D, Cunnings AJ, Pipe JG, Evelhoch JL, Soulen RL. Direct magnetic resonance determination of aortic distensibility in essential hypertension: relation to age, abdominal visceral fat, and in situ intracellular free magnesium. *Hypertension* 1997; **30**:654–659.
20 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.
21 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: a prospective study. *Lancet* 2001; **358**:1400–1404.
22 Mackey RH, Sutton-Tyrrell K, Vaitkevicius PV, Sakkinen PA, Lyles MF, Spurgeon HA, *et al*. Correlates of aortic stiffness in elderly individuals: a subgroup of the Cardiovascular Health Study. *Am J Hypertens* 2002; **15**:16–23.
23 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.
24 Oren S, Grossman E, Frohlich ED. Arterial and venous compliance in obese and nonobese subjects. *Am J Cardiol* 1996; **77**:665–667.
25 Gallagher D, Visser M, Sepulveda D, Pierson RN, Harris T, Heymsfield SB. How useful is body mass index for comparison of body fatness across age, sex, and ethnic groups? *Am J Epidemiol* 1996; **143**: 228–239.
26 Deurenberg P. Limitations of the bioelectrical impedance method for the assessment of body fat in severe obesity. *Am J Clin Nutr* 1996; **64**:449S–452S.
27 Bussolotto M, Ceccon A, Sergi G, Giantin V, Beninca P, Enzi G. Assessment of body composition in elderly: accuracy of bioelectrical impedance analysis. *Gerontology* 1999; **45**:39–43.
28 Mooy JM, Grootenhuis PA, de Vries H, Valkenburg HA, Bouter LM, Kostense PJ, Heine RJ. Prevalence and determinants of glucose intolerance in a Dutch caucasian population. The Hoorn Study. *Diabetes Care* 1995; **18**:1270–1273.
29 de Vegt F, Dekker JM, Jager A, Hienkens E, Kostense PJ, Stehouwer CD, *et al*. Relation of impaired fasting and postload glucose with incident type 2 diabetes in a Dutch population: The Hoorn Study. *JAMA* 2001; **285**:2109–2113.
30 Kelly R, Fitchett D. Noninvasive determination of aortic input impedance and external left ventricular power output: a validation and repeatability study of a new technique. *J Am Coll Cardiol* 1992; **20**:952–963.
31 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.
32 Van Bortel LM, Duprez D, Starmans-Kool MJ, Safar ME, Giannattasio C, Cockcroft J, *et al*. Clinical applications of arterial stiffness, Task Force III: recommendations for user procedures. *Am J Hypertens* 2002; **15**: 445–452.
33 Nichols WW, O'Rourke MF. *McDonald's blood flow in arteries*. 4th ed. London: Arnold, E; 1998.
34 Blacher J, Guerin AP, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness on survival in end-stage renal disease. *Circulation* 1999; **99**:2434–2439.
35 van Dijk RA, van Ittersum FJ, Westerhof N, van Dongen EM, Kamp O, Stehouwer CD. Determinants of brachial artery mean 24 h pulse pressure in individuals with Type II diabetes mellitus and untreated mild hypertension. *Clin Sci (Lond)* 2002; **102**:177–186.
36 Stergiopulos N, Westerhof N. Role of total arterial compliance and peripheral resistance in the determination of systolic and diastolic aortic pressure. *Pathol Biol (Paris)* 1999; **47**:641–647.
37 Stergiopulos N, Meister JJ, Westerhof N. Evaluation of methods for estimation of total arterial compliance. *Am J Physiol* 1995; **268**: H1540–1548.
38 Chemla D, Hebert JL, Coirault C, Zamani K, Suard I, Colin P, Lecarpentier Y. Total arterial compliance estimated by stroke volume-to-aortic pulse pressure ratio in humans. *Am J Physiol* 1998; **274**:H500–505.
39 Pauca AL, O'Rourke MF, Kon ND. Prospective evaluation of a method for estimating ascending aortic pressure from the radial artery pressure waveform. *Hypertension* 2001; **38**:932–937.
40 Smulyan H, Siddiqui DS, Carlson RJ, London GM, Safar ME. Clinical utility of aortic pulses and pressures calculated from applanated radial-artery pulses. *Hypertension* 2003; **42**:150–155.
41 Henry RM, Kostense PJ, Bos G, Dekker JM, Nijpels G, Heine RJ, *et al*. Mild renal insufficiency is associated with increased cardiovascular mortality: The Hoorn Study. *Kidney Int* 2002; **62**:1402–1407.
42 Spijkerman AM, Adriaanse MC, Dekker JM, Nijpels G, Stehouwer CD, Bouter LM, Heine RJ. Diabetic patients detected by population-based stepwise screening already have a diabetic cardiovascular risk profile. *Diabetes Care* 2002; **25**:1784–1789.
43 Eckel RH, Wassef M, Chait A, Sobel B, Barrett E, King G, *et al*. Prevention Conference VI: Diabetes and Cardiovascular Disease: Writing Group II: pathogenesis of atherosclerosis in diabetes. *Circulation* 2002; **105**:e138–143.
44 Rutter MK, Parise H, Benjamin EJ, Levy D, Larson MG, Meigs JB, *et al*. Impact of glucose intolerance and insulin resistance on cardiac structure and function: sex-related differences in the Framingham Heart Study. *Circulation* 2003; **107**:448–454.
45 Lyon CJ, Law RE, Hsueh WA. Minireview: adiposity, inflammation, and atherogenesis. *Endocrinology* 2003; **144**:2195–2200.
46 Yudkin JS, Stehouwer CD, Emeis JJ, Coppack SW. C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? *Arterioscler Thromb Vasc Biol* 1999; **19**:972–978.
47 Verma S, Li SH, Wang CH, Fedak PW, Li RK, Weisel RD, Mickle DA. Resistin promotes endothelial cell activation: further evidence of adipokine–endothelial interaction. *Circulation* 2003; **108**:736–740.
48 Okamoto Y, Arita Y, Nishida M, Muraguchi M, Ouchi N, Takahashi M, *et al*. An adipocyte-derived plasma protein, adiponectin, adheres to injured vascular walls. *Horm Metab Res* 2000; **32**:47–50.
49 Ciccone M, Vettor R, Pannacciulli N, Minenna A, Bellacicco M, Rizzon P, *et al*. Plasma leptin is independently associated with the intima–media thickness of the common carotid artery. *Int J Obes Relat Metab Disord* 2001; **25**:805–810.
50 Rebuffe-Scrive M, Enk L, Crona N, Lonnroth P, Abrahamsson L, Smith U, Bjorntorp P. Fat cell metabolism in different regions in women. Effect of menstrual cycle, pregnancy, and lactation. *J Clin Invest* 1985; **75**: 1973–1976.
51 Arner P. Differences in lipolysis between human subcutaneous and omental adipose tissues. *Ann Med* 1995; **27**:435–438.
52 Frayn KN. Adipose tissue as a buffer for daily lipid flux. *Diabetologia* 2002; **45**:1201–1210.
53 Arner P. Regional differences in protein production by human adipose tissue. *Biochem Soc Trans* 2001; **29**:72–75.
54 van Harmelen V, Dicker A, Ryden M, Hauner H, Lonnqvist F, Naslund E, Arner P. Increased lipolysis and decreased leptin production by human omental as compared with subcutaneous preadipocytes. *Diabetes* 2002; **51**:2029–2036.
55 Motoshima H, Wu X, Sinha MK, Hardy VE, Rosato EL, Barbot DJ, *et al*. Differential regulation of adiponectin secretion from cultured human omental and subcutaneous adipocytes: effects of insulin and rosiglitazone. *J Clin Endocrinol Metab* 2002; **87**:5662–5667.
56 Dusserre E, Moulin P, Vidal H. Differences in mRNA expression of the proteins secreted by the adipocytes in human subcutaneous and visceral adipose tissues. *Biochim Biophys Acta* 2000; **1500**:88–96.