Fat Distribution and Arterial Stiffness

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Increases in central fat and decreases in peripheral fat masses are associated with accelerated arterial stiffening in healthy adults

The Amsterdam Growth and Health Longitudinal Study

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ABSTRACT

Background: Central fatness is associated with higher arterial stiffness, a mechanism that may explain adiposity-related increases in cardiovascular risk. In contrast, peripheral fat and lean masses may counteract such adverse effects, but evidence for this contention, as derived from longitudinal studies at the general population level, is lacking.

Objective: To investigate the associations between changes in central (i.e. trunk) fat vs. peripheral (i.e. limbs) fat and lean masses with changes in arterial stiffness.

Design: Longitudinal study among 277 (145F) healthy adults in whom body composition (dual-energy x-ray absorptiometry) and arterial stiffness estimates (ultrasound imaging), were measured repeatedly at the ages of 36 and 42 years.

Results: Changes (per 10Kg) in trunk fat were positively whereas changes in peripheral fat were inversely associated with the carotid's Young's elastic modulus (in 10^3•kPa) [β=0.14 (95%CI: 0.02; 0.25) and -0.16 (-0.30; -0.01)] and the carotid-femoral pulse wave velocity (in m/s) [β=1.54 (0.02; 3.07) and -1.46 (-3.48; 0.56), respectively]. Individuals whose levels of trunk fat increased *and* of peripheral fat decreased over the 6-yr follow-up (33% of the study population), were those who displayed the steepest increases in these stiffness estimates. Notably, these changes were accompanied by minor increases in body weight, which remained within the limits of a normal-range throughout.

Conclusions: Increases in trunk and decreases in peripheral fat masses are associated with accelerated arterial stiffening. These findings emphasize the importance of assessment of regional changes in body composition as it may enable identification of individuals with an unrecognized increased cardiovascular risk.

INTRODUCTION

Adiposity-related increases in arterial stiffness have been proposed as one of the potential pathways through which (central) obesity could lead to cardiovascular disease (CVD) [1,2]. Arterial stiffness is an independent predictor of CVD [3,4] as it impairs the ability of the arterial system to handle the pressure boost at systole. This leads to increased systolic blood pressure, decreased diastolic blood pressure, increased left ventricular mass, and decreased diastolic perfusion [5].

Many cross-sectional studies have indeed shown that higher levels of body fatness, in particular a central pattern of fat distribution [6-9], are positively associated with arterial stiffness [6-18]. These associations are not confined to individuals with overweight or obesity, but are seen across the entire range of levels of body mass/fatness [7,11,12,16,17], and have been shown across all age categories [11,17], including children [10,13,16] and young adults [7,11,12], suggesting that higher levels of (central) adiposity do not need to be long lasting to have deleterious effects on arterial stiffness. In this line, the detrimental role of excessive body mass has been emphasized by one observational longitudinal study showing positive associations of 2-yr weight-changes with changes in arterial stiffness [19], and several small intervention studies, all confined to individuals with obesity or diabetes, showing arterial de-stiffening after weight-loss programs [20-24].

Arterial changes related to weight-changes do not enable an appreciation of the underlying changes in body composition responsible for the effects observed, however. Specifically, how changes in body composition, i.e. in central *but also* in peripheral fat and lean masses, observed during the course of ageing, and at the general population level, impact on changes in arterial stiffness, remains unknown. Notably, and in contrast to central fat, higher levels of peripheral fat, which is stored mainly subcutaneously, and lean masses may both have an independent favourable impact on arterial stiffness [7,25] as well as on other cardiovascular risk factors [25-28]. It is thus conceivable that adverse changes in body composition occur, i.e. increases in central combined with decreases in peripheral fat masses, without being reflected by changes in total body weight or weight relative to height (BMI), though both contributing additively to accelerated arterial stiffening. How changes in

peripheral fat (and lean) masses relate to changes in arterial stiffness has never been examined, however.

We have therefore examined these issues thoroughly in a cohort of apparently healthy adults, in whom measures of body composition and of local and regional arterial stiffness were measured at the ages of 36 and 42 years.

SUBJECTS AND METHODS

Study population and design

Data were derived from the *Amsterdam Growth and Health Longitudinal Study*, an observational longitudinal study that started in 1976 with a total inclusion of 698 boys and girls [29]. Its initial goal was to describe the natural development of growth, health and lifestyle of adolescents, and to investigate longitudinal relationships between biological and lifestyle variables. The mean age of the subjects at the beginning of the study was 13.1 (±0.8) years. Since then, subjects have been measured 3 to 9 times during a 30-year follow-up period. At each measurement, anthropometrical, biological and lifestyle variables were assessed, as detailed elsewhere [29]. In 2000, when the subjects' mean age was 36.6 (±0.6) years, the following measurements were added to the study for the first time: body composition by means of dual-energy x-ray absorptiometry (DXA) and properties of three large arteries by non-invasive ultrasound imaging. Complete DXA and arterial data as well as important covariates were obtained in 336 individuals attending this measurement round (baseline in the present study) [12]. More recently, in 2006, complete follow-up assessments of both body composition and large artery properties were obtained in 277 of these individuals, who constitute the study population for the present study. Baseline characteristics from the 59 individuals without follow-up data did not differ from those included, however (data not shown). Subjects included in the present study did not differ from drop-outs with regard to body fatness (BMI) and other biological risk factors at the beginning of the study (in 1976), and thereafter, indicating representativeness for the original cohort (data not shown).

The medical ethical committee of the VU University Medical Center in Amsterdam approved the study protocol and all participants gave their written informed consent.

Anthropometry and DXA

Measurements of body height and weight were performed according to standard procedures as detailed previously [7,12]. Body mass index was calculated as body weight (kg) divided by body height squared (m^2). Total and regional (arms, legs, trunk and head) body fat and lean masses were measured with a whole body DXA scanner (in 2000: Hologic QDR-2000, software version V5.67A; Hologic Inc, Walthan, USA; in 2006: Hologic QDR-4500A, software version 8.21, Hologic, Brussels, Belgium). Peripheral fat and lean masses were calculated by adding the fat or lean masses of the legs to that of the arms, respectively [7]. Given the systematic underestimation of fat mass and overestimation of lean mass obtained by the Hologic QDR-4500A as compared with the QDR-2000 device (by ~5%), data obtained with the QDR-4500A device were calibrated according to the equations provided by Schoeller et al [30].

Arterial stiffness

Arterial properties for the estimation of arterial stiffness were assessed according to guidelines for user procedures and with the use of reproducible and valid ultrasound imaging methods and devices [3,31,32]. Measures obtained in the year 2006 followed the exact same protocol as conducted in 2000 as has been described in detail elsewhere [12,33-35]. Briefly, all subjects abstained from smoking and caffeine-containing beverages on the day the measurements were performed. At the time of measurements of arterial properties, subjects had been resting in a supine position for 15 minutes in a quiet, temperature-controlled room. Properties of the right common carotid, the common brachial and the femoral arteries were obtained by trained vascular sonographers with the use of an ultrasound scanner equipped with a 7.5-MHz linear array probe (Pie Medical, Maastricht, the Netherlands). The ultrasound scanner was connected to a personal computer equipped with an acquisition system and a vessel wall movement detector software system (Wall Track System 2 (WTS_2), Pie Medical, Maastricht, the Netherlands). This integrated device enables measurements of arterial diameter (D), distension (ΔD), pulse wave transit

time (TT) and intima-media thickness (IMT) as detailed elsewhere [31]. The carotid artery was measured approximately 10 mm proximal to the beginning of the bulb, the brachial artery approximately 20 mm above the antecubital fossa and the common femoral artery 20 mm proximal to the flow divider. The exact distance was video-recorded and a print-out was obtained in order to ensure that follow-up measures, as obtained in 2006, were obtained at the exact same arterial site.

Throughout the entire period of ultrasound imaging and while the subjects were in a supine position, systolic (SBP), diastolic (DBP), mean arterial pressure (MAP) and resting heart rate were assessed in the left arm at 5-minutes intervals with an oscillometric device (in 2000: Colin Press-Mate, model BP-8800, Komaki-City, Japan; in 2006: Dinamap ProCare, GE Healthcare, Tampa, Florida, USA). Brachial artery pulse pressure (PP) was defined as SBP-DBP, and PP at the level of the common carotid and femoral arteries was calculated by calibration of the diameter-distension waveforms obtained at these arteries and at the brachial artery as described by Van Bortel *et al* [36].

Local estimates of arterial stiffness

The mean D, ΔD, and local PP of 3 consecutive measurements (each including 3 to 7 heart beats) were used to estimate the distensibility (DC) and compliance (CC) coefficients in the carotid and femoral artery, as follows [12,33-35]:

$$DC = (2\Delta D * D + \Delta D^2)/(PP * D^2) \quad \text{in } 10^{-3}/\text{kPa} \quad (1)$$

$$CC = \pi * (2D * \Delta D + \Delta D^2)/4PP \quad \text{in } mm^2/\text{kPa} \quad (2)$$

DC reflects the elastic properties, whereas the CC reflects the buffering capacity of the artery at given operating local pressures. From carotid D, DC and IMT, the Young's elastic modulus (YEM), an estimate of the intrinsic elastic properties of the vessel wall, was calculated as follows:

$$YEM = D/(IMT * DC) \quad \text{in } 10^3\text{kPa} \quad (3)$$

Note that, in contrast to DC and CC, higher values of the YEM indicate greater arterial stiffness.

Regional estimates of arterial stiffness

The carotid-femoral pulse wave velocity (cfPWV, in m/s) was measured by dividing the length between the carotid and the femoral arterial sites by the carotid-to-femoral TT (calculated by subtracting the travel time of the pressure wave from the heart to the femoral artery by that from the heart to the carotid artery) [12,35]. For technical reasons (mainly faulty ECG triggering), cfPWV was obtained only in 226 subjects (117 women) of the 277 subjects included in the present study. Levels of (changes) in trunk and peripheral fat mass, peripheral lean mass, and local arterial stiffness estimates of these subjects did not differ from the 51 subjects with missing PWV data, however (data not shown).

Reproducibility

Prior to the 2006 measurement round we conducted a pilot reproducibility study to investigate the inter-observer coefficients of variation (CVs) between the sonographers involved in the baseline (I.F.) and the follow-up (F.S.) ultrasound data collection in 2000. Both sonographers measured the arterial properties of 8 apparently healthy adults. The CVs were: for diameter, 2.7% (carotid), 4.9% (brachial) and 2.2% (femoral); for distension, 9.5% (carotid), 21.0% (brachial) and 28.3% (femoral); and for carotid IMT 6.2%.

Covariates

In both the baseline and follow-up examinations we measured subjects' levels of total and HDL-cholesterol, triglycerides, and glycated hemoglobin according to standard methods [7] and obtained information on subjects' smoking and drinking status, and daily physical activity levels (expressed in metabolic equivalents - METs/week) by means of questionnaires and structured interviews [29].

Statistical analysis

Comparisons of subjects' characteristics between baseline and follow-up were performed with the use of Student's paired *t*-tests of McNemar's tests, for continuous data or proportions, respectively. Variables with a skewed distribution were $\log_e$ transformed prior to these analyses.

We used generalized estimating equations (GEE) to examine the associations between total body fat % and measurements on body composition/distribution and arterial stiffness estimates throughout the 6-yr follow-up period. GEE analyses take into account the correlation of repeated measurements within individuals over time, and the regression coefficients thus obtained are interpretable as cumulative correlation coefficients that combine the between-subjects (cross-sectional) and the within-subjects (longitudinal) variation of variables over time. In these GEE-analyses an exchangeable correlation structure was used. In addition, we performed linear regression analyses to investigate the associations between *changes* in study variables over the 6-yrs follow-up period; changes were calculated by subtracting scores obtained in the 2006 from those obtained in the 2000 examination.

In both the GEE and the linear regression analyses, we studied the associations, first, of (changes in) total body fat %, and, second, of (changes in) trunk fat, peripheral fat or peripheral lean mass on the one hand, with each of the arterial stiffness estimates on the other. These relationships were adjusted for sex, height, (changes in) mean arterial pressure and (changes in) the other body composition variables (model 1), and further for (changes in) biological risk factors (i.e. total-to-HDL cholesterol ratio, triglycerides, glycated haemoglobin and resting heart rate) (model 2) and (changes in) lifestyle variables (smoking, alcohol and physical activity) (model 3). Effect modification by sex was analyzed by adding interaction terms between (changes in) each body composition variable and sex to the regression models described above. Because no significant interactions were found all results are presented for men and women combined.

All statistical analyses were performed using the Statistical Package for Social Sciences for Windows (SPSS version 17.0, SPSS Inc, Chicago, Illinois, USA).

RESULTS

Tables 1 and 2 show the main characteristics of the study population at baseline, and after 6-yrs of follow-up. According to their BMI values, at baseline 1.1% of the study participants were underweight (BMI<18.5 kg/m^2), 65.3% normal weight (BMI 18.5-25.0), 28.5% overweight (BMI 25-30) and 5.1% obese (BMI>30); at follow-up these values were 1.8%, 59.1%, 31.2% and 8.0%, respectively. Subjects' mean levels of body weight, BMI, trunk fat and peripheral lean masses increased and of trunk lean mass remained fairly stable in both men and women; peripheral fat mass increased in men but decreased in women.

In both men and women, the carotid IMT and the diameter of both the carotid and the femoral arteries increased whereas the distension of the carotid but not the femoral artery decreased with ageing. These changes in arterial properties, combined with decreases in (local) pulse pressure, resulted lower DC and higher YEM of the carotid artery but greater DC and CC of the femoral artery at follow-up; cfPWV increased significantly with ageing.

Table 1. General characteristics of the study population

	Men (n=132)		Women (n=145)	
	Baseline	6-yr follow-up	Baseline	6-yr follow-up
Age, yrs	36.5 ± 0.6	42.6 ± 0.6	36.6 ± 0.6	42.6 ± 0.6
Anthropometry				
Weight, kg	83.1 ± 10.0	85.5 ± 10.8‡	69.0 ± 10.7	71.1 ± 12.6‡
Body mass index, kg/m²	24.6 ± 2.9	25.3 ± 2.9‡	23.8 ± 3.5	24.2 ± 4.1†
Dual-energy x-ray absorptiometry				
Body fat, %	21.3 ± 6.3	23.6 ± 4.5‡	32.3 ± 7.1	31.8 ± 6.1
Trunk fat mass, kg	8.1 ± 4.4	10.2 ± 3.8‡	8.4 ± 4.0	9.5 ± 4.4‡
Trunk lean mass, kg	30.3 ± 3.3	29.9 ± 3.2	22.6 ± 2.8	22.7 ± 2.6
Peripheral fat mass, kg	8.7 ± 2.8	9.2 ± 2.5‡	13.1 ± 4.3	12.7 ± 4.5†
Peripheral lean mass, kg	26.7 ± 3.2	28.8 ± 3.3‡	17.1 ± 2.9	19.8 ± 2.9‡
Biological risk factors				
Systolic blood pressure, mmHg	121.5 ± 10.3	122.4 ± 13.5	111.8 ± 10.1	110.5 ± 12.0
Diastolic blood pressure, mmHg	67.0 ± 6.7	73.0 ± 7.5‡	63.1 ± 6.9	67.9 ± 7.5‡
Mean arterial pressure, mmHg	85.6 ± 7.5	88.5 ± 9.1‡	78.9 ± 8.0	82.0 ± 9.2‡
Pulse pressure (mmHg)	54.5 ± 5.9	49.4 ± 7.3‡	48.7 ± 5.5	42.6 ± 7.3‡
Total-to-HDL-cholesterol ratio, mmol/L	4.44 ± 1.34	3.61 ± 1.03‡	3.23 ± 0.92	2.68 ± 0.71‡
Triglycerides, mmol/L	1.3 [0.9-1.8]	1.1 [0.8-1.8]*	0.9 [0.6-1.2]	0.8 [0.7-1.2]
Glycated haemoglobin, %	5.24 ± 0.41	5.45 ± 0.52‡	5.23 ± 0.39	5.32 ± 0.24†
Heart rate, bpm	70.8 ± 12.0	60.7 ± 9.8‡	69.9 ± 10.9	62.4 ± 8.1‡
Lifestyle risk factors				
Smokers, %	25.0	17.4*	19.3	13.8*
Alcohol drinkers, %	94.6	94.7	84.7	88.9
Physical activity, 10^3METs/wk	3.34 [2.15-5.77]	2.68 [2.16-3.13]‡	4.54 [3.30-6.69]	2.78 [2.29-3.37]‡

Data are presented as mean ± SD, percentages, or median [inter-quartile range];
*P<0.05, †P<0.01, ‡P<0.001 vs. baseline, as obtained from Student's t-tests for paired continuous data or McNemar's tests for paired proportions, as appropriate.

Table 2. Large artery properties of the study population

	Men (n=132)		Women (n=145)	
	Baseline	6-yr follow-up	Baseline	6-yr follow-up
Carotid artery				
Diameter, mm	7.18 ± 0.52	7.40 ± 0.63‡	6.62 ± 0.52	6.84 ± 0.63‡
Distension, μm	620 ± 141	516 ± 123‡	520 ± 119	447 ± 116‡
Local pulse pressure, mmHg	52.4 ± 7.9	44.7 ± 10.8‡	45.8 ± 7.5	40.0 ± 9.5‡
Intima-media thickness, mm	0.62 ± 0.10	0.66 ± 0.12‡	0.63 ± 0.10	0.66 ± 0.11†
Distensibility coefficient, 10^{-3}/kPa	26.1 ± 5.5	25.3 ± 7.3	27.2 ± 6.5	26.2 ± 7.1
Compliance coefficient, mm^2/kPa	1.06 ± 0.28	1.09 ± 0.35	0.94 ± 0.26	0.96 ± 0.29
Young's Elastic Modulus, 10^3•kPa	0.47 ± 0.13	0.49 ± 0.16	0.42 ± 0.12	0.44 ± 0.16
Femoral artery				
Diameter, mm	10.60 ± 1.01	10.96 ± 1.07‡	9.03 ± 1.05	9.20 ± 1.20†
Distension, μm	209 ± 97	220 ± 98	230 ± 101	235 ± 99
Local pulse pressure, mmHg	53.7 ± 9.3	50.1 ± 13.5‡	49.6 ± 9.9	43.5 ± 10.7‡
Distensibility coefficient, 10^{-3}/kPa	5.7 ± 2.8	6.6 ± 3.5†	8.1 ± 4.0	9.6 ± 4.8‡
Compliance coefficient, mm^2/kPa	0.50 ± 0.24	0.61 ± 0.32‡	0.51 ± 0.24	0.63 ± 0.33‡
Central arterial stiffness				
Pulse Wave Velocity (m/s)[a]	8.11 ± 1.55	8.64 ± 1.48†	7.52 ± 1.55	8.11 ± 1.46‡

Data are presented as mean ± SD; *P<0.05, †P<0.01, ‡P<0.001 vs. baseline as obtained from Student's paired *t*-tests; [a] Data available on 226 subjects only (109 men/117 women).

Associations between body composition and arterial stiffness (GEE analyses)

Throughout the 6-yr longitudinal period, greater levels of total body fat % were adversely associated with all stiffness estimates of the carotid artery but only with the CC of the femoral artery (Table 3, model 1). The associations with the carotid but not the femoral stiffness estimates were independent of other cardiovascular risk factors (model 2). Detailed examination of the role of trunk fat, peripheral fat and lean masses suggested that greater levels of trunk, but not of peripheral fat, were adversely associated with carotid and femoral stiffness, whereas peripheral lean mass was favourably associated with stiffness levels, especially of the femoral artery. In addition, opposite and independent associations were observed between trunk (adverse) and peripheral (favourable) fat on the one hand, and cfPWV on the other [regression coefficient (b) per 10 kg increase in trunk or peripheral fat of 1.03 m/s (95% CI: 0.48 to 1.58) and -1.08 m/s (-1.67 to -0.50), respectively, $p<0.001$ for both]; the similar strength but opposite direction of these associations thus explained the lack of a significant adverse association between total body fat % and this regional stiffness estimate. Further adjustment for lifestyle factors did not materially change any of the results mentioned above (data not shown).

Associations between *changes* in body composition and *changes* in arterial stiffness

Changes in trunk fat were positively (i.e. adversely) and changes in peripheral fat mass were inversely (i.e. favourably) associated with changes in carotid YEM and in cfPWV. In addition, changes in peripheral lean mass showed a trend-wise favourable association with both carotid YEM and cfPWV (Table 4, model 1). These associations were independent of (and their magnitude remained practically unchanged after adjustments for) concomitant changes in other biological (model 2) and lifestyle risk factors (data not shown). The similar strength, but opposite direction, of associations between changes in trunk and peripheral fat with changes in these stiffness estimates again explains the observed lack of significant associations between changes in total body fat % and changes in arterial stiffness. Likewise, these associations would also not be captured if changes in carotid YEM or cfPWV were examined as a function of changes in body weight [+0.00 10^3•kPa (-0.03 to 0.04) and -0.04 m/s (-0.17 to 0.10) per 10Kg increase, respectively] - Figure 1A and B. Changes in body composition were not associated with changes in femoral stiffness estimates.

To gain further insight into the occurrence of different phenotypes of changes in body fat distribution, their distinct association with arterial stiffness and the extent to which such phenotypes would be captured by measures of changes in body weight or BMI, we divided subjects into 3 groups: A- those whose absolute levels of both trunk and peripheral fat decreased (i.e. if changes in these variables were both <0 Kg; 22% of the study participants); B- those whose levels of both trunk and peripheral fat increased (i.e. if changes in these variables were both >0 Kg; 47%); and C- those whose levels of trunk fat increased but peripheral fat decreased; 30%) (*Please see Supplementary Figure and Table for details on distribution and cross-tabulation of changes in trunk and peripheral fat*). Decreases in levels of trunk fat with concomitant increases in levels of peripheral fat were observed in 3 individuals only, who we excluded from these analyses.

After adjustments for sex, height, changes in MAP, lean mass and other biological risk factors, those with the phenotype C were those who exhibited the steepest increases in mean levels of both the carotid YEM [+0.04 10^3•kPa (0.01 to 0.08)] and the cfPWV [+0.91m/s (0.50 to 1.33)] - Figure 2A and B. Importantly, these adverse associations were observed despite the marginal and significantly lower 6-yr mean increases in body weight in these than those observed in individuals with phenotype B [+1.4 (0.5 to 2.3) *vs.* 5.0 kg (4.3 to 5.7)], respectively, Figure 3A]. Furthermore, and on the basis of their mean BMI values at both baseline and follow-up, only the individuals with phenotype B exceeded, at follow-up, the cut-off value indicative of overweight (≥25kg/m^2), whereas those with phenotype C remained within the normal-weight range throughout (Figure 3B).

Table 3. Associations of total body fat %, trunk fat, peripheral fat and peripheral lean masses with arterial stiffness throughout the 6-yr follow-up period

Arterial stiffness estimate		Total body fat % (per 10%)		Trunk fat mass (per 10kg)		Peripheral fat mass (per 10kg)		Peripheral lean mass (per 10kg)	
	Model	b	95% CI	b	95% CI	b	95% CI	b	95% CI
Carotid artery									
Distensibility coefficient (10^{-3}/kPa)	1	-1.57	-2.42; -0.72‡	-2.35	-4.32; -0.38*	-0.24	-2.56; 2.08	0.88	-1.35; 3.11
	2	-1.31	-2.20; -0.42†	-1.80	-4.00; 0.37	-0.37	-2.79; 2.05	-0.11	-2.56; 2.33
Compliance coefficient (mm^2/kPa)	1	-0.05	-0.09; -0.01†	-0.06	-0.16; 0.04	-0.04	-0.15; 0.07	0.16	0.06; 0.27†
	2	-0.04	-0.08; -0.00*	-0.03	-0.14; 0.08	-0.04	-0.16; 0.07	0.11	-0.01; 0.23
Young's elastic modulus (10^3•kPa)	1	0.03	0.01; 0.05†	0.05	-0.01; 0.10	0.01	-0.04; 0.05	-0.02	-0.07; 0.03
	2	0.03	0.01; 0.05†	0.04	-0.02; 0.10	0.01	-0.04; 0.05	-0.01	-0.07; 0.04
Femoral artery									
Distensibility coefficient (10^{-3}/kPa)	1	-0.38	-0.92; 0.16	-1.19	-2.42; 0.04	0.18	-1.29; 1.64	2.97	1.68; 4.26‡
	2	-0.13	-0.72; 0.45	-0.91	-2.27; 0.45	0.25	-1.31; 1.81	1.86	0.44; 3.28†
Compliance coefficient (mm^2/kPa)	1	-0.05	-0.09; -0.01*	-0.12	-0.20; -0.03†	0.01	-0.08; 0.11	0.32	0.22; 0.41‡
	2	-0.02	-0.06; 0.02	-0.08	-0.17; 0.02	0.01	-0.09; 0.11	0.21	0.11; 0.31‡
Pulse Wave Velocity (m/s)[a]	1	0.05	-0.22; 0.32	1.03	0.48; 1.58‡	-1.08	-1.67; -0.50‡	-0.14	-0.79; 0.50
	2	0.11	-0.17; 0.39	1.19	0.58; 1.80‡	-1.06	-1.66; -0.46‡	-0.41	-1.14; 0.32

b, longitudinal regression coefficient as obtained from GEE analyses; indicates difference in arterial stiffness estimate per 10% or per 10kg increase in body composition variable; CI, confidence interval; *P<0.05, †P<0.01, ‡P<0.001. [a] Data refer to 226 subjects only (117 women);
Model 1: adjusted for sex, height, mean arterial pressure and the other body composition variables (including trunk lean mass);
Model 2: model 1 + further adjustment for biological risk factors (i.e. total-to-HDL cholesterol ratio, triglycerides, glycated haemoglobin and resting heart rate).

Table 4. Associations of 6-yr *changes* in total body fat %, and trunk fat, peripheral fat and peripheral lean masses with *changes* in arterial stiffness

Arterial stiffness estimate		D total fat % (per 10%)		D trunk fat (per 10kg)		D peripheral fat (per 10kg)		D peripheral lean (per 10kg)	
	Model	b	95% CI	b	95% CI	b	95% CI	b	95% CI
Carotid artery									
Distensibility coefficient (10^{-3}/kPa)	1	-1.00	-3.12; 1.12	-4.08	-9.18; 1.02	1.42	-5.20; 8.05	3.28	-1.94; 8.50
	2	-0.83	-3.08; 1.42	-3.70	-8.93; 1.54	1.18	-5.51; 7.86	3.04	-2.21; 8.29
Compliance coefficient (mm^2/kPa)	1	-0.03	-0.11; 0.05	-0.08	-0.28; 0.12	0.00	-0.25; 0.26	0.12	-0.09; 0.32
	2	-0.02	-0.11; 0.07	-0.05	-0.25; 0.16	-0.01	-0.27; 0.26	0.11	-0.10; 0.32
Young's elastic modulus (10^3•kPa)	1	0.01	-0.03; 0.06	0.14	0.02; 0.25*	-0.16	-0.30; -0.01*	-0.10	-0.22; 0.01
	2	0.02	-0.03; 0.07	0.14	0.02; 0.26*	-0.15	-0.30; -0.00*	-0.10	-0.22; 0.02
Femoral artery									
Distensibility coefficient (10^{-3}/kPa)	1	-0.34	-1.57; 0.88	0.29	-2.65; 3.23	-2.51	-6.33; 1.32	0.40	-2.61; 3.40
	2	-0.48	-1.78; 0.82	-0.20	-3.20; 2.81	-2.40	-6.24; 1.44	0.38	-2.64; 3.39
Compliance coefficient (mm^2/kPa)	1	-0.04	-0.13; 0.05	-0.02	-0.23; 0.19	-0.16	-0.43; 0.12	-0.02	-0.23; 0.20
	2	-0.05	-0.15; 0.04	-0.05	-0.26; 0.17	-0.16	-0.43; 0.12	-0.02	-0.23; 0.20
Pulse Wave Velocity (m/s)[a]	1	0.30	-0.32; 0.91	1.54	0.02; 3.07*	-1.46	-3.48; 0.56	-1.24	-2.69; 0.20
	2	0.25	-0.42; 0.91	1.53	0.01; 3.08*	-1.49	-3.53; 0.56	-1.25	-2.72; 0.22

b, regression coefficient as obtained from linear regression analyses; indicates change in arterial stiffness estimate per 10% or per 10kg increase in body composition variable; CI, confidence interval; *P<0.05; [a] Data refer to 226 subjects only (117 women);
Model 1: adjusted for sex, height, changes in mean arterial pressure and changes in the other body composition variables (including trunk lean mass);
Model 2: model 1 + further adjustment for changes in biological risk factors (i.e. total-to-HDL cholesterol ratio, triglycerides, glycated haemoglobin and resting heart rate).

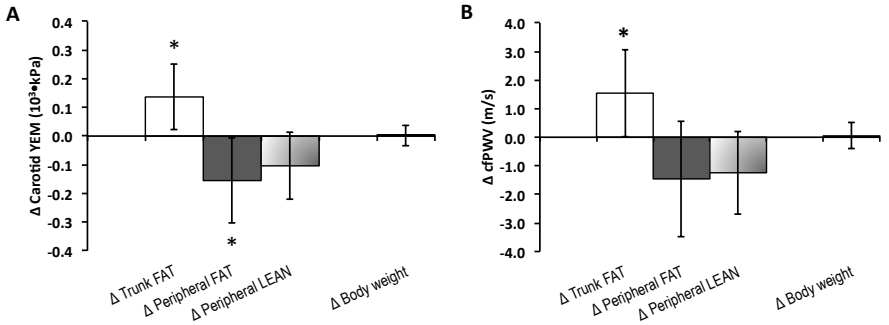

Figure 1. Bars indicate 6-yr changes in**: A)** carotid's Young's Elastic Modulus (YEM) and **B)** carotid-femoral pulse wave velocity (cfPWV), per 10kg increases in trunk fat, peripheral fat and peripheral lean masses (independent of one another and also of trunk lean mass), or per 10 kg increases in body weight; whiskers indicate 95% CI; all data are adjusted for sex, body height, and changes in mean arterial pressure as estimated by means of linear regression analyses; *P<0.05.
NOTE: data in panel A refer to 277 individuals whereas those shown in panel B are confined to a sub-set of 226 of these only (see methods section).

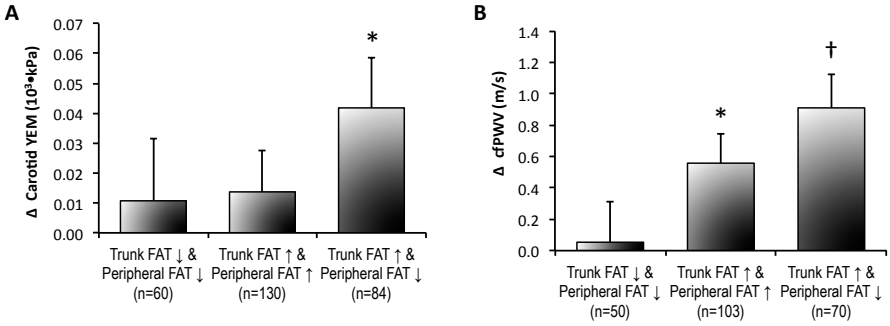

Figure 2. Bars indicate mean 6-yr changes in: **A)** carotid Young's Elastic Modulus (YEM); and **B)** carotid-femoral pulse wave velocity (cfPWV), across different phenotypes of changes in fat distribution; whiskers indicate SEM; data are adjusted for sex, body height, and changes in mean arterial pressure, lean mass and other biological risk factors as estimated by means of ANCOVA; *P<0.05, †P<0.01.
NOTE: exact *N* within each group being compared is lower in analyses shown in panel B than panel A because of missing data on cfPWV in some individuals (see methods section).

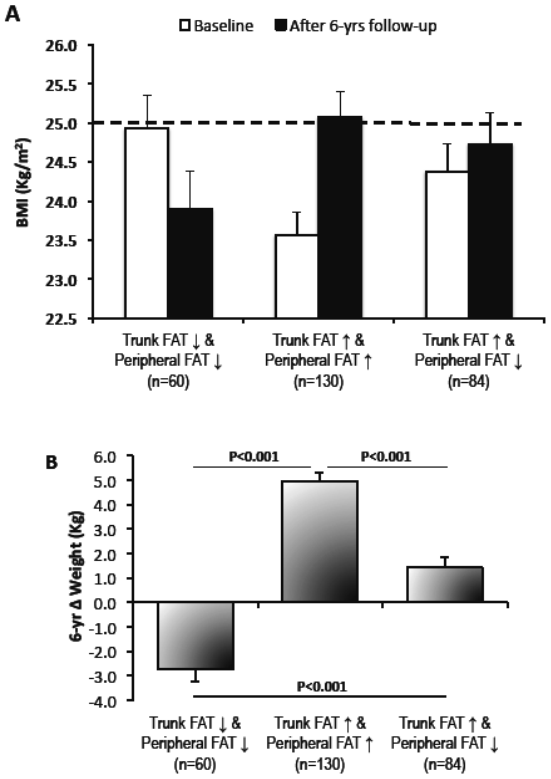

Figure 3. Bars indicate: **A)** change in body weight and **B)** BMI (at baseline and at follow-up) among individuals whose levels of both trunk and peripheral fat increased, individuals whose levels of trunk fat increased but peripheral fat decreased, and individuals whose levels of both trunk and peripheral fat decreased over the course of 6-yrs follow-up; data are adjusted for sex as estimated by means of ANCOVA; whiskers indicate SEM.

DISCUSSION

Our longitudinal study has three key findings. First, throughout the 6-yr longitudinal study, greater levels of total body fatness, particularly of trunk body fat, were *adversely* whereas peripheral lean mass was *favourably* associated with carotid and femoral stiffness. Trunk and peripheral fat also exhibited opposite associations with aortic stiffness as depicted by cfPWV. These associations were examined by means of repeated data-analyses techniques (GEE), representing the more 'chronic

(deleterious) effects' of persistent excess body fat and/or adverse fat distribution/ composition over time. Second, *changes* in trunk fat were adversely whereas *changes* in peripheral fat and lean masses were favourably associated with *changes* in the carotid and aortic, but not femoral, stiffness. These observations suggest a more 'acute' component to the deleterious 'effects' of body fat distribution and composition on arterial stiffness of predominantly elastic arterial segments. Finally, the detrimental and additive 'effects' of *increases* in trunk and *decreases* in peripheral fat masses on arterial stiffness were independent of one another and concomitant changes in lean mass and other risk factors, and accompanied by only minor increases in body weight. Importantly, this pattern of changes in body fat distribution was observed within the limits of a normal-weight range, occurred in about one third of the study population, and identified a group of individuals exhibiting the steepest increases in arterial stiffness. This is the first longitudinal study that has examined, in detail, with state-of-the art measures of both body composition and arterial stiffness, how *changes* in body fat and lean masses and their distribution correlated with *changes in* arterial stiffness as characterized by a large set of valid estimates throughout the arterial tree.

Our findings are consistent with the concept that adipose tissue accumulated centrally has more adverse effects on arterial stiffness [6-9] and cardiovascular risk than does fat stored in peripheral depots [25,26,37,38]. Our analyses of patterns of changes in body fat distribution show that such deleterious associations of a central patterning of fat accumulation are stronger when accompanied by decreases in peripheral fat, and often occur within a normal-weight range. This phenotype of (changes in) body fat distribution (C) is consistent with the existence of a relative prevalent (5 to 45%) sub-group of '(metabolically) obese but normal weight' (MONW) individuals at the population level [39,40]. In addition to elevated abdominal/visceral adiposity despite a BMI<25 kg/m^2, MONW individuals are generally characterized by altered insulin sensitivity, a more atherogenic lipid profile and/or higher levels of BP [39,40], all of which are known determinants of arterial stiffness [5]. Our data were consistent with some of these characteristics [i.e. more adverse changes in total-to-HDL cholesterol ratio [+0.29 mmol/L (0.08 to 0.51)] and HbA1c [+0.19% (0.04 to 0.33)] in the individuals who displayed this critical phenotype vs. with phenotype

A], but their comparatively steeper increases in levels of carotid and aortic stiffness were independent of changes in these risk factors. This suggests that other adiposity-related factors may be involved. Decreases in adiponectin [8,41,42], and increases in leptin [43,44], circulating proinflammatory cytokines [6], advanced glycation and/or lipoxidation products [5], and related endothelial dysfunction are likely candidates in this regard [1,2,5]. If, and the extent to which, these intertwined cellular and molecular mechanisms are stimulated differently by central vs. peripheral fat depots and explain their opposite and additive associations with arterial stiffness needs to be further examined, however. Indeed, it is becoming increasingly clear that peripheral fat depots are metabolically different from fat accumulated centrally [45], often associated with a more favourable rather than adverse metabolic/atherogenic profile [25-27]. For instance, in contrast to trunk fat, peripheral fat was linked to lower fasting and post-load glucose (26), better lipid metabolism (i.e. lower total, LDL and VLDL cholesterol, triglycerides, and higher apo-A1 and HDL cholesterol) and less aortic calcification (28).

Our findings also emphasize that determining age-related developmental changes in body size (i.e., height and weight) or weight relative to height (BMI) or even total amount of body fat relative to weight (total body fat %) is inadequate for understanding the actual changes in body composition that may lead to accelerated arterial stiffening. Although this does not diminish the value of diet and/or exercise weight-loss programs for arterial *de*-stiffening as previously shown among individuals with obesity or type 2 diabetes [20-23], it emphasizes that many other (normal weight) individuals may also be in need and can benefit from such interventions. Indeed, according to commonly used categories of body weight, they may simply be at unrecognized increased risk, and thus not targeted by adequate preventive measures. However, given their normal-weight, they may actually be more amenable and compliant to diet and exercise interventions than are obese individuals, as they will require diets with less (if any) caloric restriction and may have less physical limitations (e.g. joint, foot and respiratory problems) that hinder the performance of exercise [39].

The potential clinical relevance of our observations is also emphasized by the observed adverse associations of persistent high levels of total body fatness and of increases in trunk fat *and* decreases in peripheral fat with accelerated stiffening of the elastic carotid and aortic but not the muscular femoral arteries. Although the poorer inter-observer reproducibility with which properties of the femoral vs. the carotid arteries were measured could explain this contrast, this does not detract from the importance of our findings on the carotid artery, as stiffness of mainly elastic arteries is predictive of incident CVD and mortality [3]. A recent meta-analysis [4] estimated a 14-15% increased CVD and mortality risk per 1m/s increase in cfPWV. On the basis of these data, our estimates may translate to comparable or even greater increases or decreases in risk per 10 kg increase in trunk fat mass or decreases in peripheral fat mass in the course of 6 years, respectively (Tables 3 and 4). All together, our data support the view that adiposity-related increases in central stiffness may explain, at least in part, the increased CVD and mortality attributed to a central patterning of fat distribution.

This study has some limitations that warrant mentioning. First, the use of different DXA whole-body scanners and BP devices at both time points may have caused seemingly unexpected phenomena, such as an increase in peripheral lean mass and a decrease in PP. We attempted to circumvent the problem of systematic overestimation of body lean (and underestimation of body fat) mass with the more recent QDR 4500-A device by calibrating these data [30], but this may have not been optimal. In addition, the decreases in PP observed herein resulted from an increase (~6 mmHg) in DBP and the practically unchanged levels of SBP between the ages of 36 and 42. Although this may seem 'unexpected', increases in PP with ageing are often observed after the 5th or 6th decades of life only as a consequence of lifelong arterial stiffening [46]. Our data may thus reflect real changes among young adults. Indeed, previous life-course analyses of the two BP components in this cohort showed steeper increases in (sitting) DBP (0.6 mmHg/yr) than SBP (0.2 mmHg/yr) between late adolescence and age 36 (data not shown). Still, we cannot fully discard the possibility that the baseline DBP data may have been underestimated and/or the SBP data may have been overestimated as compared with the follow-up assessments due to improved algorithms of newer oscillometric devices (as used in the 2006 measurement

round) [47]. As a consequence, at the population level and in absolute levels, PP and all arterial stiffness estimates could have been underestimated in the 2006 vs. 2000 measurement period. Nevertheless, any systematic under- or overestimation of study variables, does not threaten the inferences arising from the associations reported herein, the strength of which were, if anything, most likely underestimated. Second, despite the fact that trunk fat as assessed by DXA correlates highly with intra-abdominal fat [48], it does not distinguish between subcutaneous and visceral fat in the trunk/abdominal region. We could thus not ascertain whether, and the extent to which, the associations of (changes in) arterial stiffness with abdominal visceral fat differed from those with (changes in) abdominal subcutaneous fat. These may need to be further examined as some studies have indeed suggested that the former are stronger than the latter [6,8,9,24]. Last, our findings were obtained in relatively young and apparently healthy Caucasian adults, and should thus be interpreted with caution with regard to older, other ethnicities, and high-risk populations.

In conclusion, changes in body composition characterized by a combination of *increases* in trunk and *decreases* in peripheral fat masses, regardless of changes in lean mass, occur relatively often, are not captured by alarmingly elevated levels of BMI or changes in body weight, but contribute to accelerated arterial stiffening. These findings, observed in young and apparently healthy adults, contribute to a better understanding of the aetiology of the widely reported adiposity-related increases in arterial stiffness. The underlying metabolic and molecular mechanisms need to be further investigated, however. Still, and from a primary prevention point of view, monitoring changes in body composition/fat distribution, focusing not only in levels of central but also of peripheral fat, may help identify those individuals who, even if within the normal-weight range, are in need and can benefit from lifestyle interventions.

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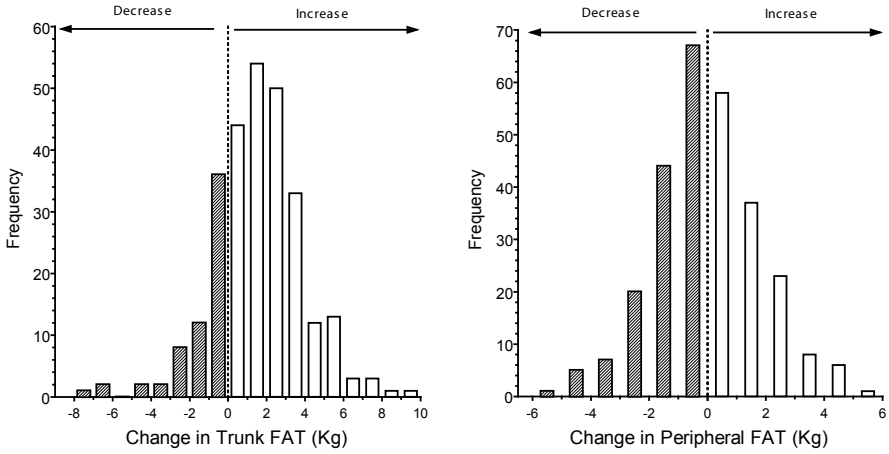

Supplemental Figure. Distribution of changes in trunk and peripheral fat mass over the 6-yr follow-up period.

Supplemental Table. Identification of different patterns of changes in body fat distribution, by cross-tabulation of changes in trunk with changes in peripheral fat mass.

Peripheral Fat Trunk Fat	Decreased	Increased	Total
Decreased	60 (16M/44F)	*3 (1M/2F)*	63 (17M/46F)
Increased	84 (33M/51F)	130 (82M/48F)	214 (115M/99F)
Total	144 (49M/95F)	133 (83M/50F)	277 (132M/145F)

M, Men; F, women