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Central and peripheral body fat distribution: Different associations with low-grade inflammation in young adults?

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Abstract *Background and aims:* Evidence regarding the impact of regional body fat distribution on low-grade inflammation is limited. The current study examined the association of central and peripheral body fat distribution and low-grade inflammation levels in young adults, considering collinearity between variables.
Methods and results: A cross-sectional analysis of 809 adults (aged 27 years) was conducted as part of the EPITeen cohort, Porto, Portugal. Regional body fat was measured by dual-energy X-ray absorptiometry scan (DXA) and serum high-sensitivity C-reactive protein (hsCRP) was measured in a fasting blood sample. OLS (ordinary least squares) and LASSO (least absolute shrinkage and selection operator) regression models were fitted to estimate the association of trunk and peripheral fat with hsCRP, stratified by sex. Using OLS regression, trunk fat in females was positively associated with ln(hsCRP) ($\beta_1 = 0.064$, 95% CI 0.018; 0.109). The effect of peripheral fat on ln(hsCRP) was shown not to be significantly different from trunk fat ($\beta_2 = -0.011$, 95% CI −0.110; 0.089), but no statistically significant association was observed ($\beta_3 = 0.053$, 95% CI −0.004; 0.110) between peripheral fat and ln(hsCRP). In males, trunk fat also showed a positive association with ln(hsCRP) ($\beta_1 = 0.104$, 95% CI 0.055; 0.154), and the effect of peripheral fat on ln(hsCRP) was shown to be significantly different from trunk fat ($\beta_2 = -0.124$, 95% CI −0.237; −0.011). However, the association between peripheral fat and ln(hsCRP) did not reach statistical significance ($\beta_3 = -0.020$, 95% CI −0.086; 0.046). The results of OLS were confirmed by LASSO regression.
Conclusion: A higher fat deposited in the trunk was positively associated with hsCRP, whereas no statistically significant effect was observed for peripheral fat.

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Introduction

Adipose tissue is a recognized endocrine organ that acts not only as a fuel storage but is also able to secrete adipokines that can modulate inflammation [1]. With increasing adiposity, adipocytes tend to enlarge, becoming hypertrophic and macrophages infiltrate adipose tissue [2]. This structural and physiological disruption of adipose tissue induces the development of a low-grade inflammatory state, which in turn, contributes to metabolic disease [3–5]. The link between adiposity profiles and inflammation can already be observed at early ages [6] and the longitudinal effect of the accumulation of adiposity on low-grade inflammation from adolescence into adulthood has been previously reported, highlighting the relevance of prevention strategies [7].

Despite the overall effect of adiposity, increasing evidence suggests that adiposity-related cardiometabolic consequences are more strongly associated with body fat distribution than with total fat deposition [8]. Adipose tissue can be divided into central and peripheral regions. Central adipose tissue includes subcutaneous fat in thoracic and abdominal regions, as well as fat in intrathoracic and intra-abdominal regions, whereas peripheral adipose tissue includes subcutaneous deposits in the upper and lower extremities [9,10].

Different mechanisms have been proposed to explain a higher metabolic activity of central fat when compared to peripheral fat. These deposits have been suggested to inherently differ in processes involving lipolysis/lipogenesis, expression of adipocyte receptors, and in the secretion of adipokines/cytokines, enzymes, hormone immune molecules, proteins and other factors [11–14]. However, it remains unclear how these physiological differences impact low-grade inflammation.

Several methods have been used to assess total and regional adiposity, mostly by indirect anthropometric measurements such as body mass index, waist, hip circumferences and skinfold thickness that, despite being simple, quick and inexpensive, are also subject to large measurement variability and reproducibility [15,16]. Direct measurements such as dual-energy X-ray absorptiometry (DXA) enable the accurate separation of body mass into fat and lean components, thereby permitting the evaluation of central and peripheral fat mass without the confounding influence of other tissue constituents [17].

In addition, there are statistical challenges regarding the best approach to model in order to distinguish the effects between central and peripheral adiposity [18]. A frequently used method to assess the associations with cardiometabolic risk factors is by examining the relative amount of regional body fat in proportion to whole body fat or to other fat regions [19–23]. However, this method can leave some residual confounding regarding total fat and, since total fat is associated with inflammation, it can induce an association in the opposite direction, hindering the true effect of trunk or peripheral fat. To overcome these limitations, there is a need to model both central and peripheral fat simultaneously. Additionally, fat regions are highly correlated with each other and with overall adiposity, weakening statistical inference when including multiple body fat regions in one model [19]. In the face of natural complexities, confounding and collinearity, model selection and predictions using traditional multivariable regression can be difficult to assess [24]. LASSO (least absolute shrinkage and selection operator) regression techniques have been found to be useful in reducing the mean square errors of parameter estimates when collinearity is present [25]. OLS (ordinary least squares) regression estimates the linear regression coefficients, minimizing the mean of the square errors, while the LASSO regression adds a term that penalizes the increase in the linear regression coefficients; the degree of penalization is tuned using cross-validation. In lay terms, LASSO penalizes the inflation of the linear regression coefficients and tends to select the most important variables amongst the ones that have collinearity.

Therefore, based on the limited and inconsistent evidence regarding the impact of regional body fat distribution on low-grade inflammatory levels [13,19,26], we used a population-based cohort to assess the association between DXA-derived central and peripheral body fat distributions with low-grade inflammatory levels, measured by high-sensitivity C-reactive protein (hsCRP), in young adults aged 27-years-old.

Methods

Study sample

Data were collected as part of the EPITeen study (Epidemiological Health Investigation of Teenagers in Porto), a population-based cohort that recruited 13-year-old adolescents born in 1990 and enrolled in the public and private schools of Porto, Portugal, during 2003/2004 [27]. Four subsequent study waves took place when participants were on average aged 17, 21, 24 and 27-years of age. For this study, we used data only for those evaluated in the fifth study wave. Of the 914 measurements with DXA, we excluded 20 exams that contained artifacts, which could affect the accuracy of the fat quantification (such as prosthetic devices, implants or other extraneous objects), 37 who did not undergo hsCRP measurements, and 48 whose hsCRP levels were above the 10 mg/L, which might be indicative of acute infection. Thus, the analysis was based on the information of 809 participants.

Our study complies with the Declaration of Helsinki and the Ethics Committee of Hospital São João. The Ethics Committee of the Institute of Public Health from the University of Porto approved the research protocol. Written informed consent was obtained from parents and adolescents in the first and second study waves, and from participants in the following study waves.

Body fat measurement

Total body fat and regional body fat mass (trunk, arms, legs) were measured using DXA (Hologic Discovery QDR®

4500 W Series, Inc., Bedford, MA), and analyzed with Hologic APEX Software, v.3.3.0.1, by trained staff according to standard operating procedures. The machine's calibration was performed every morning using a calibration phantom (Hologic DXA Quality Control Phantom, serial #24089). All subjects stayed in metal free underwear or with disposable gowns and were asked to remove all jewelry and other accessories that could interfere with the DXA exam. Body composition scans were performed with the subject in the supine position, in the center of the scan field, with the hands in prone position and the feet with internal rotation. DXA acquisition average time was approximately 7 min (varying according to individual height).

Trunk region included the neck, chest, abdominal and pelvic areas. Its upper boundary was the inferior edge of the chin and the lower borders intersect the middle of the femoral necks without touching the inferior brim of the pelvis. Peripheral fat was calculated by adding the fat mass of the legs to that of the arms. The leg region included all of the area below the lines that form the lower borders of the trunk. The arm region was comprised of the arm and shoulder area formed by placing a line from the fold of the axilla and through the glenohumeral joint. Leg measurement was assessed by the sum of both legs including thigh and calf; and arm measurement was indicated as the sum of both sides' upper arms and forearms values [28].

High sensitivity C-reactive protein

A venous blood sample was drawn after an overnight fast. All the samples were analyzed at the central laboratory of the Centro Hospitalar São João. HsCRP values were determined through particle-enhanced immunonephelometry using an auto-analyzer – Behring, Nephelometer II, BN II® (Siemens, Lisboa, Portugal). The lowest limit of detection was 0.2 mg/L. Values below the limit (5.5% of the sample) were assigned the value of 0.1 mg/L. HsCRP presented a skewed distribution to which a logarithmic transformation was applied.

Covariates

Data on covariates was collected using self-reported questionnaires. Alcohol consumption was classified as daily drinking (drinks at least once a day), occasional drinking (drinks less than once a day and former drinkers) and non-drinking. Participants were classified as daily smokers (smoke at least once a day), occasional smokers (smokers less than once a day, former smokers, and just tried) and non-smokers. Leisure-time physical activity was evaluated according to a closed four-choice question of subjective intensity categories (mainly sitting, mainly standing, active or very active) [29]. Chronic diseases were assessed by asking the question 'Do you currently have any illness requiring regular medical care?' If the answer was positive, information was gathered on type of disease. Oral contraceptive pill use was assessed by asking the question 'Do you use or have ever used an oral contraceptive (pill)?' and medicine administration was assessed by asking the question 'During the past 12 months have you taken any medications on an ongoing basis?' If the answer was positive, information was gathered on type of medication, namely analgesic (ATC code N02B) or anti-inflammatory medication (ATC codes A07E, M01A, R06A and S01B) which we used as a covariate in the analysis.

Statistical analysis

Summary descriptive statistics were calculated. Analyses were stratified by sex and each region of fat was divided by total body fat to create regional fat percentage. Continuous variables with skewed distributions were described using quartiles.

Bivariate Kendall's tau-b correlations were used to assess the associations between fat mass variables.

The traditional method for adjusting body fat regions for total fat in epidemiology studies is using total fat as a denominator. Even though this method has the advantage of being calculated directly for an individual without any statistical model, it also has some disadvantages. This method can leave some residual confounding regarding total fat and, since total fat is associated with hsCRP, it can induce an association in the opposite direction.

In order to take into account these problems, we started with the traditional model parameterization:

$$Ln(hsCRP) = \beta_0 + \beta_1 \frac{fat\ region}{total\ fat} \qquad \text{(Model 1)}$$

Then, two approaches were used in order to correct for residual confounding.

First, fat regions (central or peripheral) were adjusted for total fat:

$$Ln(hsCRP) = \beta_0 + \beta_1 \frac{fat\ region}{total\ fat} + \beta_2 total\ fat \qquad \text{(Model 2)}$$

Second, the following model was used to assess the best exponential:

$$Ln(fat\ region) = \beta_{0e} + \beta_{1e} ln(total\ fat)$$

$$\Leftrightarrow ln(fat\ region) - \beta_{1e}\, ln(total\ fat) = \beta_{0e}$$

$$\Leftrightarrow ln(fat\ region) - ln\left(total\ fat^{\beta 1e}\right) = \beta_{0e}$$

$$\Leftrightarrow Ln\left(\frac{fat\ region}{total\ fat^{\beta 1e}}\right) = \beta_{0e}$$

Thus, the estimated exponential ($\widehat{\beta}_{1e}$) was used to obtain the following model:

$$Ln(hsCRP) = \beta_0 + \beta_1 \frac{fat\ region}{total\ fat^{\widehat{\beta 1e}}} \qquad \text{(Model 3)}$$

Total fat was then included in the model to adjust for any residual confounding left:

$$Ln(hsCRP) = \beta_0 + \beta_1 \frac{fat\ region}{\widehat{total\ fat}^{\beta 1e}} + \beta_2\ total\ fat \qquad \text{(Model 4)}$$

However, because total fat is associated with hsCRP, the ratios could still be confounded. Therefore, to assess whether there was a different effect of fat according to body region (trunk vs. peripheral), the following models were estimated:

Model 5, which assumes that the effect of fat on hsCRP is the same regardless of whether it comes from trunk or peripheral fat:

$$Ln(hsCRP) = \beta_0 + \beta_1\ total\ fat \qquad \text{(Model 5)}$$

Since *Total fat* ≈ *peripheral* fat + trunk fat, the following model can be rewritten as following:

$$Ln(hsCRP) = \beta_0 + \beta_1\ peripheral\ fat + \beta_1\ trunk\ fat$$

and

Model 6, which assumes that the effect of fat on hsCRP is different according to the region (trunk vs. peripheral):

$$\begin{aligned} &Ln\ (hsCRP) = \beta_0 + \beta_1\ total\ fat \\ &+ \beta_2\ peripheral\ fat \Leftrightarrow Ln\ (hsCRP) = \beta_0 + \beta_1\ peripheral\ fat \\ &+ \beta_1\ trunk\ fat + \beta_2\ peripheral\ fat \Leftrightarrow Ln\ (hsCRP) = \beta_0 \\ &+ \underbrace{(\beta_1 + \beta_2)}_{\beta_3}\ peripheral\ fat + \beta_1\ trunk\ fat \end{aligned} \qquad \text{(Model 6)}$$

All models were estimated with the Ordinary Least Squares (OLS) regression [regression coefficients (β), 95% confidence intervals (95% CI)]. However, due to the strong correlation between the independent variables, the analysis with OLS might be flawed. The variance inflation factor (VIF) was calculated to assess collinearity [30]. In addition, the last model (Model 6) was performed using LASSO regression procedures that account for multicollinearity [30]. It has several advantages over conventional methods, especially because it allows the selection of variables even when there is collinearity among variables. The usefulness of the method rests not only upon its ability to produce good parameter estimates, with smaller mean squared error than OLS, but also on having reasonable inferential procedures [25,31].

Statistical analyses were performed using the Statistical Package for the Social Sciences (IBM® SPSS® Statistics), version 25.0 and the glmnet package from the R package, version 3.0.1. Statistical significance was considered if p was lower than 0.05.

Results

Characteristics of the study sample, by sex, are presented in Table 1. Compared to males, females showed higher total fat mass, leg fat %, peripheral fat %, and hsCRP concentrations. By contrast, males presented higher trunk fat %.

Table 2 displays the bivariate Kendall's tau-b correlations between adiposity measurements. In both sexes, all adiposity variables were highly correlated.

The linear regression models fitted to examine separately the associations of trunk-to-total fat ratio and peripheral-to-total fat ratio with ln(hsCRP) levels, by sex, are presented in Table 3. After further adjustment for total fat and after correcting for residual confounding (Model 4), trunk-to-total fat ratio showed a positive association with ln(hsCRP), while peripheral-to-total fat ratio showed an inverse association in both sexes. However, the associations remained statistically significant only in males (β = 0.11, 95% CI 0.02; 0.22 for trunk-to-total fat ratio and −0.02, 95% CI −0.04;−0.00 for peripheral-to-total fat ratio).

Table 4 presents the associations of trunk and peripheral fat with ln(hsCRP) obtained using OLS and LASSO techniques, which allows both types of adiposity in the same model despite the high collinearity. With the OLS procedure, trunk fat in females was significantly associated with an increase in ln(hsCRP) (β_1 = 0.064, 95% CI 0.018; 0.109). The effect of peripheral fat on ln(hsCRP) was shown not to be significantly different from trunk fat (β_2 = −0.011, 95% CI −0.110; 0.089), but when we estimated the effect of peripheral fat and ln(hsCRP), no statistically significant association was observed (β_3 = 0.053, 95% CI −0.004; 0.110). In males, trunk fat also showed a positive association with ln(hsCRP) (β_1 = 0.104, 95% CI 0.055; 0.154), and the effect of peripheral fat on ln(hsCRP) was shown to significantly differ from trunk fat (β_2 = −0.124, 95% CI −0.237;−0.011). However, the association between peripheral fat and ln(hsCRP) did not reach statistical significance (β_3 = −0.020, 95% CI−0.086; 0.046). In the OLS regression, a VIF of 11.04 was seen in females and of 17.44 in males. Yet, the results of OLS were further confirmed by LASSO regression, which accounts for collinearity.

Discussion

When analyzing the association between trunk-to-total fat ratio and peripheral-to-total fat ratio with ln(hsCRP) in separate models, central fat was shown to be positively associated with ln(hsCRP), whereas peripheral fat presented the opposite effect in males. No statistically significant associations were observed for either trunk-to-total fat and peripheral-to-total fat ratios in females. However, when analyzing the effects of both trunk and peripheral fat in the same model, and using an approach that takes into account the collinearity between different components of adiposity, trunk fat was associated with increasing levels of inflammation in both sexes, while peripheral fat was shown to have no statistically significant effect. The lack of association observed for peripheral fat does not suggest that it has a protective effect but that it is less pro-inflammatory than trunk fat.

This study extends the understanding of the relationships between regional fat distribution and low-grade inflammatory risk, by investigating the relationships in a

Table 1 Characteristics of the study sample, by sex.

	Females	Males	*p*
	n = 401 (49.6%)	n = 408 (50.4%)	
Age, years	26.7 (0.5)	26.8 (0.4)	0.089
Alcohol consumption, n (%)			
Non-drinker	45 (12.0)	25 (6.5)	**0.026**
Occasional drinker	317 (84.5)	341 (88.8)	
Daily drinker	13 (3.5)	18 (4.7)	
Smoking frequency, n (%)			
Non-smoker	203 (51.9)	181 (45.4)	**0.032**
Occasional smoker	114 (29.2)	112 (28.1)	
Daily smoker	74 (18.9)	106 (26.6)	
Leisure-time physical activity, n (%)			
Mainly sitting	85 (21.2)	115 (28.2)	**<0.001**
Mainly standing	162 (40.4)	112 (27.5)	
Active	142 (35.4)	148 (36.3)	
Very active	12 (3.0)	33 (8.1)	
Chronic disease (any), n (%)			
No	209 (72.7)	325 (79.9)	**0.017**
Yes	109 (27.3)	82 (20.1)	
Anti-inflammatory medication, n (%)			
No	388 (97.0)	396 (97.3)	0.800
Yes	12 (3.0)	11 (2.7)	
Oral contraceptive pill, n (%)			
No	119 (29.7)	NA	
Yes	214 (60.1)	NA	
Body fat measurement			
BMI, kg/m^2	21.9 (20.4–23.9)	23.8 (21.9–25.9)	**<0.001**
Total fat mass, kg	21.5 (17.7–25.8)	19.2 (14.9–23.82)	**<0.001**
Total fat, %	37.94 (33.4–42.8)	26.7 (21.5–31.5)	**<0.001**
Trunk fat mass, kg	8.8 (6.8–11.6)	8.7 (6.6–11.8)	0.376
Trunk fat, %	41.9 (5.1)	47.4 (4.4)	**<0.001**
Peripheral fat mass, kg	11.5 (9.8–13.7)	9.0 (6.9–10.9)	**<0.001**
Peripheral fat, %	53.3 (4.5)	45.9 (3.8)	**<0.001**
Arm fat mass, kg	2.4 (1.8–2.9)	2.0 (1.6–2.6)	**<0.001**
Arm fat, %	10.8 (1.4)	10.7 (1.2)	0.162
Leg fat mass, kg	9.1 (7.8–10.9)	6.9 (5.3–8.4)	**<0.001**
Leg fat, %	42.6 (4.7)	35.2 (3.8)	**<0.001**
HsCRP, mg/L	1.4 (0.6–3.3)	0.8 (0.4–1.6)	**<0.001**

HsCRP, high-sensitivity C-reactive protein. NA, not applicable.
Values are expressed as mean (SD) or median (25–75th percentiles). For each variable, the total may not add to 809 due to missing data.
Significant results are highlighted in bold.

Table 2 Bivariate Kendall's tau-b correlations between regional body fat distribution and total fat, by sex.

		Total fat mass, kg	Trunk fat mass, kg	Peripheral fat mass, kg	HsCRP, mg/L
		Females			
Total fat mass, kg	Males	–	0.847	0.818	0.263
Trunk fat mass, kg		0.887	–	0.665	0.265
Peripheral fat mass, kg		0.860	0.748	–	0.245
HsCRP, mg/L		0.270	0.276	0.247	–

A $p < 0.001$ was observed for all the correlations.

population-based sample of young adults with DXA imaging of adipose deposits of both trunk and peripheral fat. Previous studies have shown that regional fat accumulation has a stronger correlation with cardiometabolic disease than total adiposity [19,32,33]. Our results agree with contribute to explain these differences since we have found a pro-inflammatory effect of trunk fat while peripheral fat showed a more neutral effect, after accounting for the effect of total adiposity. Increasing evidence has shown that peripheral fat deposits are metabolically different from fat accumulated centrally, often associated with a more favorable rather than adverse metabolic profile [10,13,19,22,23,34]. Additionally, a study has shown that in vivo interleukin (IL)-6 release from gluteofemoral adipose tissue was lower than from abdominal subcutaneous adipose tissue in both men and women [13]. The latter findings suggest that lower-body adipose tissue may have a more beneficial inflammatory phenotype.

Table 3 Linear regression results obtained by ordinary least squares reporting beta coefficients for elevated ln(hsCRP) levels per increase in trunk-to-total fat ratio and peripheral-to-total fat ratio, by sex.

	Females	
	β	95% CI
Trunk fat		
Trunk fat/total fat		
Model 1. Crude	**0.06**	**0.04; 0.08**
Model 2. Adjusted[a]	0.01	−0.01; 0.04
Trunk fat/(total fat)$^{1.24}$ (95% CI 1.21;1.27)		
Model 3. Crude	0.17	−0.15; 0.49
Model 4. Adjusted[a]	0.12	−0.18; 0.42
Peripheral fat		
Peripheral fat/total fat		
Model 1. Crude	**−0.05**	**−0.08;−0.03**
Model 2. Adjusted[a]	0.00	−0.03; 0.02
Peripheral fat/(total fat)$^{0.87}$ (95% CI 0.84;0.90)		
Model 3. Crude	−0.00	−0.01; 0.01
Model 4. Adjusted[a]	−0.00	−0.01; 0.01
	Males	
	β	95% CI
Trunk fat		
Trunk fat/total fat		
Model 1. Crude	**0.07**	**0.05; 0.10**
Model 2. Adjusted[a]	0.01	−0.01; 0.04
Trunk fat/(total fat)$^{1.14}$ (95% CI 1.12;1.16)		
Model 3. Crude	**0.13**	**0.02; 0.22**
Model 4. Adjusted[a]	**0.11**	**0.02; 0.22**
Peripheral fat		
Peripheral fat/total fat		
Model 1. Crude	**−0.04**	**−0.07;−0.02**
Model 2. Adjusted[a]	**−0.03**	**−0.05;−0.00**
Peripheral fat/(total fat)$^{0.97}$ (95% CI 0.95;0.99)		
Model 3. Crude	**−0.02**	**−0.04;−0.01**
Model 4. Adjusted[a]	**−0.02**	**−0.04;−0.00**

Each value represents beta coefficient derived from a separate regression model.
Significant results are highlighted in bold.
[a] Further adjusted for total fat.

Table 4 Linear regression estimated by OLS and LASSO to evaluate the association of total fat and peripheral fat with ln(hsCRP), by sex.

	Females	
	β	95% CI
Model 5		
Trunk fat (kg) (β1)	**0.059**	**0.045; 0.072**
Peripheral fat (kg) (β1)	**0.059**	**0.045; 0.072**
Model 6		
OLS		
Trunk fat (kg) (β1)	**0.064**	**0.018; 0.109**
Peripheral fat (kg) (β3)	0.053	−0.004; 0.110
$\beta 2 = \beta 3 - \beta_1$	−0.011	−0.110; 0.089
LASSO		
Trunk fat (kg) (β1)	0.058	
Peripheral fat (kg) (β3)	0.059	
$\beta 2 = \beta 3 - \beta_1$	0.001	
	Males	
	β	95% CI
Model 5		
Trunk fat (kg) (β1)	**0.052**	**0.040; 0.064**
Peripheral fat (kg) (β1)	**0.052**	**0.040; 0.064**
Model 6		
OLS		
Trunk fat (kg) (β1)	**0.104**	**0.055; 0.154**
Peripheral fat (kg) (β3)	−0.020	−0.086; 0.046
$\beta 2 = \beta 3 - \beta_1$	**−0.124**	**−0.237;−0.011**
LASSO		
Trunk fat (kg) (β1)	0.098	
Peripheral fat (kg) (β3)	−0.013	
$\beta 2 = \beta 3 - \beta_1$	−0.111	

Significant results are highlighted in bold.
OLS, ordinary least squares; LASSO, least absolute shrinkage and selection operator; CI, confidence interval.

Additionally, our results support a more relevant role of central fat beyond total adiposity in men than in women after adjustment for total adiposity. By contrast, total adiposity seems to have a stronger impact in women, also confirmed by previous evidence [35].

There are a limited number of studies with a similar accurate regional assessment of body fat in relation to hsCRP to which we can draw parallels. In a study conducted in 150 postmenopausal women, the authors found that while abdominal fat mass percentage displayed the strongest correlation with hsCRP, no significant correlations were found between indices of peripheral adiposity and hsCRP levels after adjusting for total adiposity [23]. However, women who have reached menopause tend to accumulate in the visceral depot and, due to hormonal factors, might present different mechanisms for its association with hsCRP. For example, CRP levels have been found to be higher in premenopausal women than in men, presumably due to the increasing effect of estrogens on CRP concentrations [36]. These higher levels of hsCRP in women compared to men suggest that women are at higher risk for developing cardiovascular diseases and preventive strategies are warranted. In addition, hormonal replacement therapy has been shown to increase CRP concentrations [37]. Regarding the premenopausal stage, a study performed in Canadian adults using computed tomography (CT) reported that CRP levels were largely influenced by visceral adiposity in men, whereas subcutaneous adiposity was the key correlate of CRP in women [38]. However, the study only assessed central adiposity levels. In the present study, we found a positive association between the use of oral contraceptive pills and hsCRP levels in females, but there was no statistically significant association between oral contraceptive pills and body fat parameters. Additionally, we tested physical activity, smoking and the presence of a chronic disease as potential confounders, but the results did not change. Therefore, these variables were not used as confounders in the final analysis.

Central fat has been suggested to be an anatomic manifestation of 'adiposopathy' (i.e. sick fat) and, thereby, detrimental to cardiovascular health [2,39]. The adverse effects of central adiposity have been suggested to arise from the combination of subcutaneous adipose tissue dysfunction and the accumulation of visceral adipose tissue. The particular importance of visceral versus

subcutaneous fat accumulation has been increasingly challenged, as there is growing evidence suggesting that visceral adipocytes are phenotypically different from subcutaneous adipocytes. Differences in expression of adipokine genes and in secretion in vitro are well established when comparing subcutaneous and visceral fat [40]. However, little is known regarding differences between upper- and lower-body fat. Benign multiple symmetrical lipomatosis is manifested by increased fat accumulation in the subcutaneous adipose tissue regions of the arms, legs, shoulders, and neck. Typically, glucose or lipid disorders do not develop in these patients, a finding most likely due to increased proliferation of small adipocytes in subcutaneous adipose tissue and the increased secretion of anti-inflammatory adipokines, such as adiponectin [41].

A limitation of this study is its cross-sectional design that restricts inference with regard to causality. In addition, DXA did not allow for the separate quantifications of visceral and subcutaneous fat in the trunk, or subcutaneous and intramuscular fat in the extremities. However, the regional fat measurement using DXA is reliable compared to CT, a gold standard tool for quantifying and comparing regional fat amounts [42]. It also has the ability to scan whole body fat distribution with low radiation exposure, short scanning time, high precision and low cost. Furthermore, because most of the associations have been ascertained using conventional anthropometrics with limitations in providing accurate measurements of regional fat mass, the need to use more refined imaging techniques to accurately quantify fat distribution on a large scale has been identified [43,44].

In addition, we relied on a single hsCRP measurement, but this inflammatory biomarker has been shown to be stable with little or no diurnal variation [45,46]. CRP is a clear marker of cardiometabolic risk [47] and has consistently been shown to predict cardiometabolic disease in multiple prospective epidemiological studies [45,48,49]. It is a marker of underlying low-grade inflammation that was shown to add prognostic information on cardiovascular risk comparable to blood pressure or cholesterol, and current guidelines recommend its assessment for cardiovascular risk stratification [50–52]. CRP is released mainly from the liver after cytokine stimulation [53] and it is usually selected due to its analytical advantages and stability concerning short-term fluctuations [46,54,55].

The large sample size of young adults, the population-based approach, the use of DXA to assess regional body fat and the novelty of using a different methodological approach to measure the association of trunk and peripheral fat with CRP are strengths of this study.

In conclusion, using data from a population-based sample of young adults, we observed that higher fat deposited in the trunk was positively associated with hsCRP levels, whereas no statistical significant effect was observed for peripheral fat. These findings, observed in young and apparently healthy adults, emphasize the relevance of body fat distribution in enabling the early identification of individuals with an unrecognized increased cardiovascular disease risk.

Declaration of interests

None.

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