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Ability of adiposity indicators to identify elevated high-sensitivity C-reactive protein in young adults

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ABSTRACT

Objective: The aim of the present study was to compare the discriminatory ability of different adiposity indicators in distinguishing subclinical inflammatory levels in individuals 21 y of age.
Methods: Data from the EPITeen (Epidemiological Health Investigation of Teenagers in Porto) population-based cohort (N = 1547) was analyzed. Body mass index (BMI), body fat percentage (BF%), waist circumference (WC), waist-to-hip ratio (WHR), and waist-to-height ratio (WHtR) were ascertained to assess their relationship to high-sensitivity C-reactive protein (hs-CRP). Logistic regression models were fitted to examine the association of each adiposity indicator with elevated hs-CRP (≥75th sex-specific percentile). The areas under the curve (AUCs) of the receiver operating characteristic curves were calculated for all adiposity indicators to compare their relative ability to correctly classify individuals with elevated hs-CRP.
Results: After adjustment, all adiposity indicators were significantly associated with high hs-CRP in both sexes, except WHR in women (odds ratio, 1.15; 95% confidence interval [CI], 0.98–1.36). The magnitude of the associations was stronger in women. BMI presented the best discriminatory ability in women (AUC = 0.675; 95% CI, 0.632–0.717; cutoff values >22.6 kg/m^2). In men, both BF% (AUC = 0.604; 95% CI, 0.557–0.651; cutoff values >18%) and WHtR (AUC = 0.604; 95% CI, 0.557–0.651; cutoff values >0.5) showed the best discriminatory ability. On the contrary, WHR showed the least ability to discriminate high hs-CRP in both sexes (AUC = 0.539; 95% CI, 0.489–0.584 for women and AUC = 0.574; 95% CI, 0.528–0.620 for men).
Conclusion: WHR showed the least discriminatory ability for correctly identifying individuals with elevated hs-CRP. The small differences observed among the adiposity indices hinder the recommendation of a single best adiposity measure as predictor of low-grade inflammatory levels.

Introduction

The cardiometabolic risk attributed to adiposity is suggested to be mediated by the relationship between adiposity and low-grade systemic inflammation [1,2]. Although the pathophysiologic process is not completely understood, there is evidence of the participation of inflammatory factors in the early stages of atherogenesis, including impairment of endothelial function and the formation of fatty streaks and plaque, and in the thrombotic events that trigger myocardial infarction and stroke [3].

Adipose tissue acts as an active endocrine organ that releases a variety of hormones and cytokines that contribute to activate a pro inflammatory state [4,5]. Epidemiologic studies have shown a clear relationship between obesity and C-reactive protein (CRP) [6], the most widely investigated inflammatory marker related to future cardiovascular risk [7–10]. The discovery of high-sensitivity techniques, with stable plasmatic concentrations and relative low cost, has enabled the accurate detection of the presence of an underlying low-grade inflammatory state. Although there is some controversy regarding the prognostic ability of high sensitivity-CRP (hs-CRP) beyond established risk factors [11], current guidelines recommend its assessment for cardiovascular disease (CVD) risk stratification in both primary and secondary settings [9,12,13]. In addition, the guidelines underscore the importance of a life-course

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perspective on risk assessment and prevention from young adulthood in reducing the risk for atherosclerotic CVD that occurs over decades and is related to long-term and cumulative exposure to modifiable factors such as obesity [13].

Anthropometric measures to assess adiposity are widely accepted as useful tools because they are noninvasive and inexpensive methods that can be used in clinical and epidemiologic research allowing to improve the participation rate and statistical power [14,15]. However, although body mass index (BMI) remains a frequently used index to define adiposity status, it does not distinguish between lean and fat mass [16]. In addition, techniques such as bioelectric impedance, with estimates of body fat percentage (BF%), are used to provide information on overall adiposity, but they do not permit the assessment of fat mass distribution [17]. Therefore, other anthropometric indicators have been used to identify patterns of fat distribution.

Waist circumference (WC), a measure of both subcutaneous and visceral fat, is easily measured and often is used as a measure of visceral fat in epidemiologic studies. However, WC is also correlated with body frame size, and the ratio of WC to hip circumference (HC; waist-to-hip ratio [WHR]) often is used instead [18]. HC, however, has restraints as an index of frame size because in addition to measuring "horizontal" pelvic bone size, it also measures pelvic subcutaneous fat mass and muscle mass. Height is a measure of body frame size, thus the waist-to-height ratio (WHtR) has been proposed as an alternative to the WHR and has been advocated as being slightly superior in terms of the prediction of metabolic disturbances in adults and children [19–21]. However, there is debate over the most appropriate adiposity markers of obesity-associated health risks, and evidence comparing the relationship between WHtR and other adiposity indicators with hs-CRP levels is scant [22].

Moreover, the relationship between adiposity indicators and CRP levels has been described in older adults [23–26]. Often, this estimate is confounded by factors that appear later in life, such as medical illness and treatment, which create complexity [27]. Less is known regarding the comparability of different adiposity indicators and hs-CRP in young adulthood [28], which could be of interest as early and specific indicators of future adiposity-related manifestation.

Hence, the present study aimed to compare the discriminatory ability of different adiposity indices (BMI, BF%, WC, WHR, and WHtR) in distinguishing subclinical inflammatory levels, measured by hs-CRP, in young adults 21 y of age.

Methods

Participants

Data was collected as part of the EPITeen study (Epidemiological Health Investigation of Teenagers in Porto), a population-based cohort that recruited 13-y-olds born in 1990 and enrolled in public and private schools of Porto, Portugal, during 2003 to 2004 [29]. A second evaluation took place between 2007 and 2008 and a third evaluation between 2011 and 2013, when participants were on average 17 and 21 y of age, respectively. The cohort comprises 2942 participants but, for this study, we used data from the third study wave (2011–2013).

In the third study wave, 1764 participants were re-evaluated. Of these, 28 did not perform the anthropometric measurements, 74 did not undergo blood collection, 64 were not considered for the analyses because they presented hs-CRP levels >10 mg/L, which might be indicative of acute infection, and 51 were excluded because they were taking analgesic or anti-inflammatory medication. Thus, the analysis was based on the information of 1547 participants.

The present study complied with the Declaration of Helsinki and the Ethics Committee of Hospital S. João and 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 third study wave.

Anthropometrics

Weight and height were obtained with the individual wearing lightweight indoor clothing and no shoes. Weight was measured in kilograms, to the nearest tenth, using a digital scale, and height was measured in centimeters, to the nearest tenth, according to standardized procedures. WC and HC were measured to the nearest 0.1 cm with a flexible and non-distensible tape, avoiding exertion of pressure on the tissues and with the participant standing. WC was measured midway between the lower limit of the rib cage and the iliac crest, at the end of gentle expiration, and HC was measured on the maximum circumference over the femoral trochanters. BF% was estimated by foot-to-foot bioelectrical impedance (Tanita TBF-300, Tanita Corporation of America, Inc, Arlington Heights, IL, USA).

High-sensitivity C-reactive protein

A venous blood sample was drawn after an overnight fast at each study wave. All the samples were analyzed at the central laboratory of the Hospital S. João. hs-CRP levels were determined through particle-enhanced immunonephelometry using an auto-analyzer Behring, Nephelometer II, BN II (Dade Behring Marburg GMBH, Germany). The lowest limit of detection was 0.2 mg/L. Values below the detection limit (10.5% of the sample) were assigned the value of 0.1 mg/L. Sex-specific high hs-CRP levels were considered ≥75th percentile (3.1 mg/L for women and 1.1 mg/L for men).

Covariates

Data on covariates was collected using self-reported questionnaires. Participant education was assessed as the last completed schooling year. 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 classified as "sitting," "standing and/or walking (without running)," and "very active,"

Statistical analysis

Continuous variables were presented as mean standard deviation (SD) or median (25th–75th percentiles) and Student's *t* test or Mann–Whitney U test was used for two-group comparisons. Proportions were compared using χ^2 tests.

Separate logistic regression models (odds ratios [ORs], 95% confidence interval [CI]) were fitted to examine the association of each adiposity indicator with elevated hs-CRP (≥75th sex-specific percentile), adjusting for potential confounders (education, leisure-time physical activity, and smoking habits). For comparison of the magnitude of effect, a Box–Cox transformation followed by a *z*-score transformation stratified by sex were performed to standardize all adiposity indicators. This allowed us to estimate the increase in hs-CRP levels by the SD of each adiposity indicator.

The areas under the curve (AUCs) of the receiver operating characteristic curves were calculated for all adiposity indicators to compare their relative ability to correctly classify individuals with a high level of hs-CRP. A value of 1 would suggest perfect (100% discrimination), whereas 0.5 (the diagonal) would indicate discrimination that is no better than chance. Cutoff points were defined according to Youden's index [30] as the point on the curve where the sum of sensitivity and specificity was highest. The non-parametric method was used to test whether the AUCs of the adiposity indicators were different [31].

Statistical analyses were stratified by sex and were performed using SPSS version 23 (IBM, Armonk, NY, USA), and the R package version 3.0.1. The α critical value of 0.05 was considered to define statistical significance.

Results

Characteristics of participants regarding lifestyle, adiposity indicators, and hs-CRP levels are presented in Table 1. Compared with the women, men presented more smoking habits and higher BMI, WC, WHR, and WHtR. On the contrary, women showed higher educational levels, higher leisure-time physical activity levels, BF%, and hs-CRP concentrations (Fig. 1).

Table 2 presents the logistic regression models fitted to examine the associations between each adiposity indicator and high hs-CRP, by sex. After adjustment for potential confounders, all adiposity indicators were significantly associated with high hs-CRP in both sexes, except WHR in women. The magnitude of the associations was stronger in the women. For both women and men, ORs were greatest for BF% (OR, 1.99; 95% CI, 1.65–2.39 in women; OR, 1.58; 95% CI, 1.34–1.87 in men) and lower for WHR (OR, 1.15; 95% CI, 0.98–1.36 in women; OR, 1.27; 95% CI, 1.08–1.50 in men).

Table 1
Descriptive information on lifestyle, adiposity indicators, and hs-CRP levels of participants, by sex*

	Women	Men	*P*-value
Overall, n (%)	784 (50.7)	763 (49.3)	–
Age, y	21.9 (0.5)	21.9 (0.4)	0.354
Education, n (%)			
≤12 y	233 (29.8)	306 (40.5)	<0.001
13–14 y	208 (26.6)	223 (29.5)	
≥15 y	340 (43.5)	227 (30)	
Leisure-time physical activity, n (%)			
Sitting	245 (31.4)	272 (35.8)	<0.001
Standing and/or walking	388 (49.7)	294 (38.7)	
Very active	148 (19)	193 (25.4)	
Smoking frequency			
Non-smokers	259 (33.3)	190 (25.1)	<0.001
Occasional smokers	334 (42.9)	327 (43.2)	
Daily smokers	185 (23.8)	240 (31.7)	
BMI (kg/m^2)	21.5 (19.8–23.8)	23 (21.1–25.5)	<0.001
BF%	24 (19.4–29.1)	14.1 (10.8–18.1)	<0.001
WC (cm)	71.6 (67.1–77)	80.1 (75.3–86.1)	<0.001
WHR	0.8 (0.7–0.8)	0.8 (0.8–0.9)	<0.001
WHtR	0.4 (0.4–0.5)	0.5 (0.4–0.5)	<0.001
hs-CRP, (mg/L)	1.1 (0.5–3.1)	0.6 (0.3–1.1)	<0.001
hs-CRP, n (%)†			
<1 mg/L	370 (47.2)	534 (70)	<0.001
1–3 mg/L	209 (26.7)	168 (22)	
>3 mg/L	205 (26.1)	61 (8)	

BF%, body fat percentage; BMI, body mass index; hs-CRP, high-sensitivity C-reactive protein; WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio.
*Continuous variables are presented as mean (standard deviation) or median (25th–75th percentiles). For each variable, the total may not add to 1547 owing to missing data.
†hs-CRP classified according to Ridker [9].

The areas under the ROC curves (AUCs) and the cutoff points for overall and central adiposity anthropometric indicators to identify high hs-CRP levels and the respective cutoff values are summarized in Table 3. BMI presented the best discriminatory ability for women (AUC = 0.675; 95% CI, 0.632–0.717), with high hs-CRP suggested by BMI cutoff values >22.6 kg/m^2, followed by BF% (AUC = 0.673; 95% CI, 0.629–0.717) and WHtR (AUC = 0.650; 95% CI, 0.606–0.695). In men, both BF% (AUC = 0.604; 95% CI, 0.557–0.651) and WHtR (AUC = 0.604; 95% CI, 0.557–0.651) showed the best discriminatory ability, with high hs-CRP suggested by BF% cutoff values >18% and WHtR cutoff values >0.5. By contrast, WHR showed the least ability to discriminate in both sexes (AUC = 0.539; 95% CI, 0.489–0.584 for women and AUC = 0.574; 95% CI, 0.528–0.620 for men). Whereas in women the AUC for WHR was statistically different from the others and WC was statistically different from BMI and BF%, in men, similar AUCs were observed among the five adiposity indicators.

Discussion

In this population-based study of young adults, all adiposity indicators were strongly associated with elevated hs-CRP levels in both women and men, except WHR in women. In addition, the magnitude of the associations for all adiposity indicators was shown to be stronger in women. WHR presented the least ability to discriminate high hs-CRP. All the other adiposity indicators presented a similar discriminatory ability. Considering both sexes, WHtR and BF% were shown to have the best ability in identifying individuals with elevated hs-CRP levels.

Although BMI is a widely used anthropometric index to evaluate the effects of obesity on cardiometabolic risk factors, its accuracy in detecting excess adiposity in the general population is limited because it cannot measure body fat directly and it poorly distinguishes among total body fat, total body lean mass, and bone mass [16]. To overcome misclassifications, direct measurements of BF% have been used with more sophisticated and expensive equipment such as bioelectrical impedance. However, these logistical constraints prevent it from being considered as a first stage indicator. Still, in this study, BF% was the adiposity indicator that was

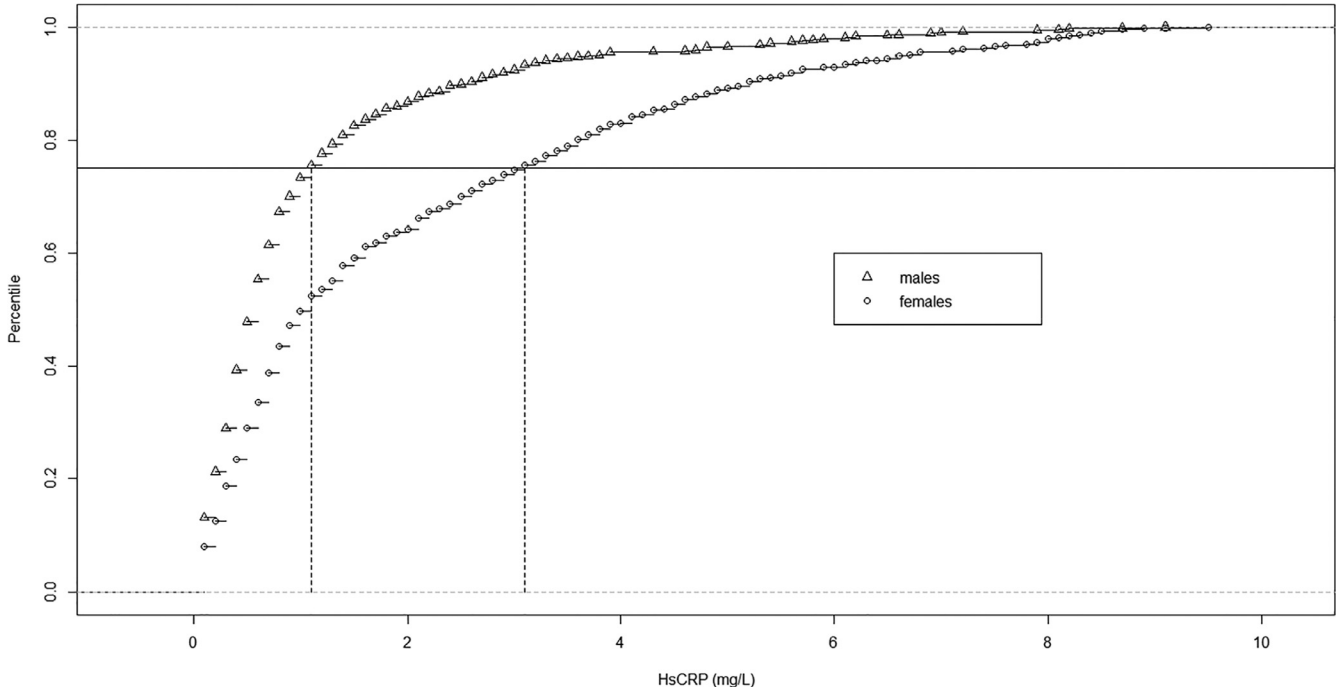

Fig. 1. Percentile of hs-CRP according to sex, with the 75th percentile (3.1 mg/L for women and 1.1 mg/L for marked) marked by solid line. hs-CRP, high-sensitivity C-reactive protein.

Table 2
OR of high levels of hs-CRP (≥75th sex-specific percentile) per 1 standard deviation increase in each adiposity indicator*

	OR (95% CI) crude		OR (95% CI) adjusted†	
	Women	Men	Women	Men
zBMI	1.91 (1.60–2.29)	1.50 (1.27–1.78)	1.86 (1.56–2.22)	1.52 (1.29–1.79)
zBF%	1.95 (1.63–2.34)	1.55 (1.32–1.84)	1.99 (1.65–2.39)	1.58 (1.34–1.87)
zWC	1.64 (1.39–1.96)	1.47 (1.25–1.74)	1.63 (1.38–1.92)	1.53 (1.30–1.80)
zWHR	1.14 (0.97–1.34)	1.28 (1.09–1.51)	1.15 (0.98–1.36)	1.27 (1.08–1.50)
zWHtR	1.70 (1.44–2.02)	1.51 (1.28–1.79)	1.71 (1.44–2.03)	1.56 (1.32–1.85)

BF%, body fat percentage; BMI, body mass index; CI, confidence interval; hs-CRP, high-sensitivity C-reactive protein; OR, odds ratio; WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio *Each value represents OR (95% CI) derived from a separate regression model.
†Adjusted for education, leisure-time physical activity, and smoking status (non-smoker, occasional smoker, daily smoker).

shown to have the highest magnitude of association in both sexes, and that could best distinguish high hs-CRP levels in men followed by WHtR and in women following BMI. In a Taiwanese sample of older adults, BF% was found to be the adiposity indicator that showed the strongest association with high hs-CRP levels in both sexes compared with BMI, WC, and WHR [25].

WHR was shown to be weakly associated with high hs-CRP and to have the least discriminatory ability in both sexes. Our results suggest that BMI, BF%, and WHtR presented a slightly higher AUC in women, whereas BF% and WHtR showed better discriminatory ability in men. The authors of the Women's Health Study found that BMI and WC were strongly associated with CRP levels, whereas a weaker association was observed for WHR [23]. Similar results were observed in healthy, middle-aged Dutch women [32] and among US adults [33]. However, none of these studies investigated WHtR.

WC and BMI are highly correlated and when considered individually reflect the extent of both central and overall adiposity. WHR and WHtR are less strongly related to BMI than WC and are therefore more specific surrogates for fat distribution. Although WHR and WHtR may be preferred as predictors of adverse levels of low-grade inflammation, owing to the lower potential for collinearity, WC has been used more often as an adiposity indicator because it is easier to measure and interpret [34,35]. However, WC does not consider stature, which might underestimate the relative amount of abdominal fat in short individuals and overestimate in those who are tall. Despite WHR being a fairly good adiposity index, hip circumference (HC) is not always taken accurately, given the difficulty in ascertaining the morphologic points, thereby, measurement errors of both methods (WC and HC) might be adding up. In addition, proportional changes in WC and HC may not change WHR despite changes in body size, whereas WHtR changes only when WC decreases or increases. By adjusting for height, the individual corpulence is taken into account (owing to genetics and growth) despite changes in fatness, and is thereby more sensitive to changes in body composition. In the Bogalusa Heart Study, Srinivasan et al. underscored the utility of WHtR in detecting central adiposity and related adverse cardiovascular risk among normal-weight younger adults, which also considered CRP levels [36]. In line with our results, studies relating adiposity indicators with different metabolic disturbances found that WHtR showed a good discriminatory ability in both sexes [19,37,38].

The cutpoints for WHtR suggested by the ROC analysis to predict high hs-CRP levels in the present study (0.5 in both sexes) are similar to the international proposed cutoff value of 0.5 [39]. Also, few other studies have evaluated the discriminatory ability of WHtR in identifying high levels of hs-CRP [22,36] and have suggested that WHtR <0.5 might protect against low-grade inflammatory levels.

Although current guidelines present the same hs-CRP cutoff for both sexes [9,12,13], several studies have found sex-different associations between obesity and CRP, and the implementation of sex-specific CRP cutoffs has been suggested for improving CVD risk assessment [6]. The present study results showed low hs-CRP levels as expected and significant differences in hs-CRP according to sex, with women presenting higher concentrations than men. Therefore sex-specific cutoff points were used to consider a high degree of low-grade inflammation. In a recent study performed in adolescents [22], the authors also considered sex-specific cutoffs for high hs-CRP levels and found similar results for girls, but higher AUC in abdominal adiposity indicators for boys.

The pathophysiologic mechanisms for a sex difference remain unclear. Differences in the metabolic activity of adipose tissue may be linked to higher CRP production in women [40]. Also, anthropometric indicators of adiposity are indirect measures of body fat, and the sex difference may be partially explained by women having higher BF% and thus might have pronounced CRP synthesis [41]. However, men presented higher central adiposity, which has

Table 3
AUC (95% CI) values and cutoff points for anthropometric indicators to identify hs-CRP high levels (≥75th sex-specific percentile)

	Women hs-CRP ≥ 3.1 mg/L				Men hs-CRP ≥ 1.1 mg/L			
	AUC (95% CI)	Cutoff point	Sensitivity	Specificity	AUC (95% CI)	Cutoff point	Sensitivity	Specificity
BMI (kg/m^2)	0.675 (0.632–0.717)*[a]	22.6	59.9	70.8	0.597 (0.551–0.644)*[a]	25.6	36.8	79.8
BF%	0.673 (0.629–0.717)*[a]	22.3	63.6	64.7	0.604 (0.557–0.651)*[a]	18	38.2	78
WC (cm)	0.640 (0.595–0.684)*[b]	71.6	66.7	55.5	0.602 (0.555–0.649)*[a]	83.8	46.1	71.2
WHR	0.539 (0.489–0.584)[c]	0.8	30.3	79.5	0.574 (0.528–0.620)*[a]	0.5	48	68
WHtR	0.650 (0.606–0.695)*[a,b]	0.5	59.1	67.6	0.604 (0.557–0.651)*[a]	0.5	45.6	72.5

AUC, area under the receiver operating characteristic curves; BF%, body fat percentage; BMI, body mass index; CI, confidence interval; hs-CRP, high-sensitivity C-reactive protein; WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio.
Different superscript letters ([a,b,c]) within each AUC indicate statistically significant differences ($P < 0.05$) between the five adiposity indicators.
*$P < 0.05$.

been suggested to have higher inflammatory properties [42]. Nevertheless, these anthropometric measures do not permit the distinction between subcutaneous or visceral adiposity, and the latter has been suggested to be responsible for a worse metabolic profile [17].

ROC analysis has emerged as a popular method for assessing the effectiveness of diagnostic tests measured on a continuous scale, independently of the cutoff point used [43]. We found AUCs of 0.54 to 0.68 (i.e., on average, a random selection from the individuals having high hs-CRP levels will have a score greater than a random selection from the individuals having normal hs-CRP levels between 54% and 68%). Although these values reflect low to moderate discriminatory ability, they are in line with other studies, reflecting that most anthropometric indices only expect to assess cardiovascular risk factors with 60% to 70% accuracy and are thus best regarded as first-stage, or population based, screening measures [19,25].

Some limitations need to be considered when interpreting these results. Although we relied on a single hs-CRP measurement, this was not expected to affect the present results because CRP levels have shown to be stable with little or no diurnal variation [44,45]. CRP is the most extensively studied and best standardized inflammatory marker related to future cardiovascular pathology [7,8,46]. It has consistently been shown to predict cardiometabolic disease in multiple prospective epidemiologic studies [44,47–50]. Despite the cross-sectional nature of the present study, we could speculate that the positive association between central adiposity and hs-CRP occurs early and could explain, at least in the part, the time course–dependent relationships between adiposity and low-grade inflammation.

Strengths of this study included the population-based approach in young adults and the possibility of ascertaining five different adiposity indicators. As obesity prevalence soars worldwide, appreciation of the close links between obesity and cardiometabolic disease increases. The finding that adiposity induces a low-grade inflammation state has fundamentally changed the view of the underlying causes and progression of obesity-related cardiovascular risk [51,52]. Each of these five adiposity indicators has been used to differently assess body fat distribution (total fat, central fat, and peripheral fat). Interestingly, there is biological plausibility that different types and distribution of body fat may play a different role in the promotion of inflammation [17], with studies suggesting that central adiposity may be more closely associated with a pro-inflammatory profile than total and peripheral adiposity [17]. 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 [53]. Examining these associations in young adulthood enables the identification of early and specific indicators of an unresolved inflammatory response induced by adiposity, thereby paving the way for optimization of prevention and treatment strategies to combat cardiometabolic disease since its onset. The present findings add to few studies that have compared the ability of different adiposity indicators to identify elevated CRP concentrations in young adults, particularly by studying five different measures that have been most used in epidemiologic studies and examining sex-specific differences.

Conclusion

In this population-based sample of young adults, WHR showed the least discriminatory ability to correctly classify individuals with elevated hs-CRP, whereas the other adiposity indicators showed similar ability. The small differences in the discriminatory ability may be of limited clinical relevance, which hinders the recommendation of a single best adiposity measure as predictor of low-grade inflammatory levels.

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