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Original article

Body adiposity indicators and cardiometabolic risk: Cross-sectional analysis in participants from the PREDIMED-Plus trial

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SUMMARY

Background & aims: Excess adiposity is associated with poor cardiometabolic (CM) health. To date, several techniques and indicators have been developed to determine adiposity. We aimed to compare the ability of traditional anthropometric, as well as standard and novel DXA-derived parameters related to overall and regional adiposity, to evaluate CM risk.

Methods: Using the cross-sectional design in the context of the PREDIMED-Plus trial, 1207 Caucasian senior men and women with overweight/obesity and metabolic syndrome (MetS) were assessed. At baseline, anthropometry- and DXA-measured parameters of central, visceral, peripheral and central-to-peripheral adiposity together with comprehensive set of CM risk factors were obtained. Partial correlations and areas under the ROC curve (AUC) were estimated to compare each adiposity measure with CM risk parameters, separately for men and women, and in the overall sample.

Results: DXA-derived indicators, other than percentage of total body fat, showed stronger correlations (rho −0.172 to 0.206, $p < 0.001$) with CM risk than anthropometric indicators, after controlling for age, diabetes and medication use. In both sexes, DXA-derived visceral adipose tissue measures (VAT, VAT/Total fat, visceral-to-subcutaneous fat) together with lipodystrophy indicators (Trunk/Legs fat and Android/Gynoid fat) were strongly and positively correlated ($p < 0.001$) with glycated hemoglobin (HbA1c), the triglyceride and glucose index (TyG), triglycerides (TG), the ratio TG/HDL-cholesterol (TG/HDL-C), and were inversely related to HDL-C levels ($p < 0.001$). Furthermore, in AUC analyses for both sexes, VAT/Total fat showed the highest predictive ability for abnormal HbA1c levels (AUC = 0.629), VAT for TyG (AUC = 0.626), both lipodystrophy indicators for TG (AUCs = 0.556), and Trunk/Legs fat for HDL-C (AUC = 0.556) and TG/HDL-C (AUC = 0.581).

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Conclusions: DXA regional adiposity measures offer advantages beyond traditional anthropometric and DXA overall adiposity indicators for CM risk assessment in senior overweight/obese subjects with MetS. In particular, in both sexes, visceral adiposity better stratifies individuals at risk for glucose abnormalities, and indicators of lipodystrophy better predict markers of dyslipidemia.

1. Introduction

Obesity, which is characterized by an excess of fat mass, is an important risk factor for developing metabolic abnormalities, type 2 diabetes (T2D) and cardiovascular (CV) disease, as well as premature death [1–3]. Therefore, it is necessary to establish new guidelines in terms of optimal body adiposity indicators to define cardiometabolic (CM) risk in clinical and research settings.

In clinical practice, an anthropometry measure — the body mass index (BMI) — is the most commonly used proxy to assess overall adiposity and identify individuals at CM risk [4]. However, subjects who are obese using BMI criteria vary in their regional body fat distribution, metabolic profile and degree of its-associated CM complications [5–7]. In this regard, excess of fat in the abdomen, and particularly of the visceral adipose tissue (VAT) depot, has been linked with greater CM risk than in peripheral area [5,6,8]. Therefore, surrogate measures of abdominal adiposity, such as the waist circumference (WC), waist-to-hip and waist-to-height ratios (WHR and WtHR, respectively), have been recommended to evaluate CM risk in clinical practice and research [9–13]. However, anthropometric measures do not distinguish between either fat and lean mass or VAT and subcutaneous adipose tissue (SAT) within the abdomen.

Dual-energy x-ray absorptiometry (DXA) represents the "gold standard" imaging technique for direct body composition analysis, enabling measures with high-precision, low radiation exposure, and short-scanning time [14]. The standard DXA procedure permits to evaluate overall and regional adiposity (arm, trunk, leg, android, and gynoid area). Moreover, an advanced application CoreScan for DXA has been developed recently, which enables validated VAT measures [15]. Previous studies have already demonstrated the ability of DXA-derived VAT to predict CM risk beyond anthropometric and standard DXA parameters (total, trunk and android fat), in young lean and obese subjects [16–18]. However, as individuals age, body fat progressively changes, resulting in fat loss from periphery and its accumulation in the central body regions [19]. In this regard, in the last years, DXA-derived ratios of central-to-peripheral adiposity (Trunk/Legs fat and Android/Gynoid fat), knowing as markers of lipodystrophy, have also been associated with risk for insulin resistance and dyslipidemia [20–22]. However, the functional advantages of a comprehensive set of adiposity indicators, ranged from simple to sophisticated, for CM risk assessment in the elderly, have not been well established so far.

Bearing in mind the aforementioned considerations, the aim of this study was to compare the ability of different body adiposity indicators to evaluate cardiometabolic risk in overweight and obese senior subjects with metabolic syndrome (MetS). Among the body adiposity indicators, we tested traditional anthropometric, as well as standard and novel DXA-derived parameters related to overall and regional adiposity.

2. Methods

2.1. Study overview and sample

This study was a cross-sectional analysis of baseline data within the framework of the ongoing PREDIMED-Plus trial, a 6-year parallel-group, multicenter, randomized clinical trial, involving 6874 participants from 23 Spanish recruiting centers. The PREDIMED-Plus trial was designed to evaluate the effect of lifestyle intervention aiming at losing weight with an energy-restricted traditional Mediterranean diet (MedDiet), physical activity (PA) promotion and behavioral support on the primary prevention of CV morbimortality. The PREDIMED-Plus recruitment period lasted from 5 September 2013 to 31 October 2016. The protocol with a detailed description of the PREDIMED-Plus trial have been described elsewhere [23] and is available on the website http://www.predimedplus.com/.

Eligible participants were senior men and women (aged 55–75 years) with overweight/obesity (BMI $\geq$ 27 and < 40 kg/m^2), who met at least three criteria for the MetS (abdominal obesity, high blood pressure, fasting glucose and triglyceride, as well as low HDL-cholesterol levels) [24]. Among criteria for the MetS, abdominal obesity was highly prevalent condition, as high WC (>88 cm for women and >102 cm for men) was detected in 96.1% of participants. Most of participants (97.5%) were of Caucasian origin. All participants provided written informed consent. The study was approved by the institutional review boards of all recruiting centers according to the ethical standards of the Declaration of Helsinki. The trial was registered at the International Standard Randomized Controlled Trial (ISRCT: http://www.isrctn.com/ISRCTN89898870) with number 89898870 and registration date of 24 July 2014.

Of the total cohort of the PREDIMED-Plus population, subsample of 1532 participants underwent total body DXA scans at baseline, in order to obtain data on body composition compartments. Of those, 1289 participants (from 6 recruiting centers) had data on VAT and SAT within the android region available. Moreover, participants with no data available on the CM risk parameters or the covariables, and whose DXA measurements exceeded planned time of DXA exploration were excluded from the analyses (n = 82) (Supplementary Fig. 1). Finally, a total of 1207 participants were included for the present study. We used PREDIMED-Plus baseline database generated in August 2017.

All participants provided written informed consent. The study was approved by the institutional review boards of all recruiting centers according to the ethical standards of the Declaration of Helsinki. The trial was registered at the International Standard Randomized Controlled Trial (ISRCT: http://www.isrctn.com/ISRCTN89898870) with number 89898870 and registration date of 24 July 2014.

2.2. Indicators of adiposity measurements: anthropometric and DXA-derived parameters

The anthropometric parameters were measured at the baseline visit by trained staff according to the PREDIMED-Plus internal procedures. Body weight (kg) and height (cm) were measured in light clothing and without shoes with use of calibrated scale and a wall-mounted stadiometer, respectively. BMI, as an indirect proxy for overall adiposity, was calculated as weight (kg) divided by square of the height (m). As far as surrogates for abdominal adiposity are concerned, WC (cm) was determined midway between the lowest rib and the iliac crest, and hip circumference (HC,

cm) was determined at the widest part. Both, WC and HC values were measured with use of an anthropometric tape and served to determine WHR. We also calculated the WtHR by division of WC by height.

Direct measures of body adiposity at baseline had to be performed preferably within 2 months from the baseline visit at which biochemical and blood pressure parameters were determined (mean ± standard deviation (SD) time difference between measurements was of 18.5 ± 30.6 days). Overall adiposity (total fat mass (g), total body fat (TBF, %)) and regional adiposity (trunk, leg, android gynoid fat mass (g)) measures were performed with DXA scanner (GE Healthcare/DXA Lunar Prodigy Primo and Lunar iDXA; Madison, WI) connected with enCore™ software using automatic total body scan mode. The regions of interest (ROI) for regional body composition were defined using the software provided by the manufacturer. Among them, the abdominal android fat ROI was defined as the area that begins at the top of the iliac crest toward the head for 20% of the distance from the iliac crest to the base of the skull. For VAT measures, scans were reanalyzed using validated CoreScan software application [15], which algorithms work through detection of the width of the SAT layer on the lateral part of the abdomen and the anterior–posterior thickness of the abdomen, by x-ray attenuation of the abdominal cavity in the android region. This is automated procedure developed by GE Healthcare [15]. In the android ROI, SAT (g) was calculated by subtracting VAT from android fat mass, as previously described [18]. Subsequently, aforementioned DXA-derived parameters were used to calculate different ratios by simple divisions of fat mass from the specific regions: Trunk/Legs fat, Android/Gynoid fat, VAT/Total fat, SAT/Total fat, VAT/SAT. DXA scans were performed by trained operators following standard protocol and subject positioning provided by the manufacturer. Participants were scanned wearing examination gown. The DXA was phantom calibrated daily according to manufacturer guidelines.

Since the anthropometric and DXA-derived adiposity indicators were recorded in different units, they became normalized into a sex-specific z-scores for analysis. This approach allowed comparing directly the risk magnitude per 1 standardized deviation (SD) change difference in the adiposity indicator.

2.3. Cardiometabolic risk parameters measurements

The parameters related to CM risk were measured at the baseline examination by trained staff. Systolic and diastolic blood pressure (SBP and DBP, mmHg) were determined in triplicate with use of validated semiautomatic oscillometer, and the average of three repeated measurements was taken into analyses. Blood samples collected after overnight fast were used to determine plasma glucose (mg/dL), glycated hemoglobin (HbA1c, %), high-density lipoprotein cholesterol (HDL-C, mg/dL), and triglyceride (TG, mg/dL) levels with use of standard laboratory enzymatic methods. Low-density lipoprotein cholesterol (LDL-C, mg/dL) was calculated using the Friedewald formula whenever TG levels were inferior to 400 mg/dL [25]. TG and HDL-C values were used to determine the TG/HDL-C ratio. The triglycerides and glucose index (TyG) was calculated using the equation: ln[TG (mg/dL) × glucose (mg/dL)/2] [26,27].

2.4. Covariables assessment

A self-reported questionnaire was used to collect the baseline data on sociodemographic factors (sex, age, education level), smoking status, medical conditions and medication use (antidiabetic, antihypertensive, cholesterol lowering). Previously validated in Spain semi-quantitative food-frequency questionnaire [28] was used to estimate alcohol intake (g/d). A 17-point score was used to assess baseline adherence to the MedDiet. A validated self-reported physical activity questionnaire (REGICOR) [29] together with codes and MET values from the 2011 Compendium of Physical Activities [30] was used to assess total leisure-time PA (METs. min/week), according to the indications described previously [23].

Dichotomous variable was generated for diabetes prevalence. Diabetic condition was defined as diagnosed diabetes self-reported at inclusion or baseline HbA1c $\geq$ 6.5% or use of antidiabetic medication at baseline, such as insulin, metformin (in case of diagnosed diabetes or Hba1c $\geq$ 6.5%) or others. Smoking status was categorized into 3 categories (current, former and never).

2.5. Statistical analyses

Descriptive statistics with means ± SDs for continuous variables or numbers (percentages) for categorical variables were used to summarize baseline characteristics of the study participants. One-way analysis of variance (ANOVA) and chi-square tests (χ^2) (for continuous and categorical variables, respectively) were used to evaluate differences in baseline socio-behavioral, body adiposity and clinical characteristics of participants according to CM risk parameters levels.

Spearman's partial correlation coefficient was used to evaluate the relationship between anthropometric, DXA-derived adiposity indicators and the parameters related to CM risk, as well as to evaluate how the measurements of overall and regional adiposity assessed by these two different methods are related to each other.

Subsequently, we selected those CM risk components and adiposity indicators with the strongest associations found in correlation analysis. Receiver operating characteristic (ROC) curve analysis under covariables was used to assess the accuracy of adiposity indicators, those selected from correlation analysis (VAT, VAT/Total fat, VAT/SAT, Trunk/Legs fat, Android/Gynoid fat) and the other that are commonly used (BMI, WC, TBF), for prediction of the binary outcome of HbA1c, TyG, TG, HDL-C and TG/HDL-C. For this we considered an abnormal condition when HbA1c $\geq$ 6.5%, TG $\geq$ 150 mg/dL, and HDL-C < 50 (for women) or <40 (for men). The cut-off threshold for TyG and TG/HDL-C was established based on the reference values found in the literature as 8.31 [31] and 3.88 [32], respectively. The area under the curve (AUC) with a 95% confidence interval (CI) were calculated.

All models (partial correlation and ROC analysis) were adjusted for the following baseline factors: recruiting center, age, and diabetes prevalence, as well as for treatment with antihypertensive (in case of SBP and DBP) and cholesterol lowering (in case of LDL-C) medications. These covariables were selected based on the prior knowledge [33,34] and specific conditions of the study. Due to the sexual dimorphism in body composition [35], the analysis was performed separately for men and women, followed by an overall analysis in a sex-adjusted model.

Moreover, we performed additional analyses using linear regression models. Three models were examined: a crude model (adjusted for recruiting center); multivariable model 1 (the same as in the correlation and ROC analysis) adjusted for recruiting center, baseline age, diabetes prevalence, treatment with antihypertensive (in case of SBP and DBP) and cholesterol lowering (in case of LDL-C) medications; and multivariable model 2 further adjusted for smoking status, alcohol intake, total leisure-time physical activity and adherence to MedDiet. Finally, to test the robustness of our findings, sensitivity analyses with the use of the linear regression multivariable model 1 were conducted: a) excluding patients with metallic prosthesis (n = 107 excluded); b) adjusting for time difference between DXA measurements and biochemical and blood pressure determinations; c) adding an interaction term to study

possible effect modification by diabetes prevalence, and stratifying diabetic (n = 346) and non-diabetic (n = 861) participants.

Statistical analyses were performed using Stata v15.0 and SPSS v17.0 programs, with statistical significances set at $p < 0.05$.

3. Results

Baseline body adiposity indicators of participants by CM risk parameters levels are shown in Table 1. Baseline socio-behavioral and clinical characteristics by CM risk parameters levels are shown in Supplementary Table 1. The participants were divided into normal and increased CM risk group according to blood pressure, TG, HDL-C and HbA1c levels. CM risk was identified using pre-defined cut-off thresholds (see footnote for Table 1). In these participants, the mean age was 65.3 ± 5.0 years and the mean BMI was 32.6 ± 3.3 kg/m^2 (data not shown in tables). Body adiposity indicators were little associated with low cholesterol HDL, and, on the other hand, high glycated hemoglobin was the CM risk factor most associated with anthropometric and DXA-derived indicators of central body fat deposition. In the present sample, BMI was not associated with any of the CM risk parameters. TBF was associated only with high TG levels, but not in the expected direction. In general, participants at CM risk were more likely to be current smokers, display T2D, had worse profile of blood levels of CM risk parameters, and spent less time on PA than those within the normal risk range.

Table 2 shows the coefficients of partial correlations between body adiposity indicators and the CM risk parameters levels, adjusted for recruitment center, age, diabetes prevalence, and treatment with medications (in case of LDL-C and blood pressure). In general, DXA-derived indicators were significantly correlated (rho −0.172 to 0.206, $p < 0.001$) with CM risk parameters. Moreover, within the DXA-derived indicators, the ratios of fatness (i.e. Trunk/Legs fat) showed stronger correlations than the crude measures of specific fat areas (i.e. Trunk fat or Legs fat alone). In men (Table 2A), the strongest positive correlations were found between indicators of visceral adiposity (VAT and VAT/Total fat mass) and HbA1c (rho 0.149 to 0.161, $p < 0.001$). In women (Table 2B), VAT and VAT/Total fat mass together with lipodystrophy indicators (Trunk/Legs fat and Android/Gynoid fat) were strongly and positively correlated with HbA1c and TyG (rho 0.163 to 0.206, $p < 0.001$), as well as with lipid levels —TG/HDL-C (rho 0.166 to 0.178, $p < 0.001$) and TG (only for VAT/Total fat; rho 0.151, $p < 0.001$). Additionally, visceral adiposity (VAT and VAT/Total fat), as well as the ratio Trunk/Legs fat were inversely related to HDL-C levels (rho −0.172 to −0.145, $p < 0.001$). In general terms, results in both sexes (Table 2C), were similar to those reported in women. Additionally, the correlations between VAT, Trunk/Legs fat, Android/Gynoid fat and TG levels were higher than in men and women analyzed separately. Similarly, for VAT/SAT in the overall sample, the correlation with HbA1c, TyG and TG/HDL-C reached higher levels of statistical significance, albeit the association was still weaker than for VAT or VAT/Total fat. The correlations between adiposity indicators and LDL-C, as well as blood pressure levels were much weaker than for other CM risk parameters. The anthropometric indicators were poorly associated with CM risk parameters, being the highest the correlations between WHR and HbA1c in women (rho 0.147, $p < 0.001$).

Results from AUC analysis for BMI, WC, TBF, VAT, VAT/Total fat, VAT/SAT, Trunk/Legs fat, and Android/Gynoid fat for prediction of an elevated levels of HbA1c, TyG, TG, HDL-C, and TG/HDL-C in the overall sample are displayed in Fig. 1. Results from sex-specific AUC analysis for aforementioned indicators are presented in Supplementary Table 2. After controlling for recruitment center, age and diabetes prevalence, all adiposity indicators showed modest ability to identify CM risk, with AUCs ranging 0.457 to 0.629. Among them, DXA-derived indicators of regional adiposity showed higher ability to predict abnormal CM risk parameters levels than anthropometric indicators or TBF. In particularly, for both sexes together, VAT/Total fat had the highest AUC for HbA1c (AUC = 0.629, 95% CI 0.567–0.690) and VAT for TyG (AUC = 0.626, 95% CI 0.578–0.674); both lipodystrophy indicators had the highest AUC for TG (AUCs = 0.556, 95% CI 0.523–0.589); and the AUC of Trunk/Legs fat was the highest for HDL-C (AUC = 0.556, 95% CI 0.523–0.584) and TG/HDL-C (AUC = 0.581, 95% CI 0.536–0.617).

Results from multivariate regression analyses, with different levels of adjustments, including other lifestyle factors (such as

Table 1
Baseline body adiposity indicators of participants by cardiometabolic risk parameters levels.

n = 1207	Blood pressure (mmHg)		P	HbA1c (%)		P	TG (mg/dL)		P	HDL-C (mg/dL)		P
	Normal CM risk	Increased CM risk		Normal CM risk	Increased CM risk		Normal CM risk	Increased CM risk		Normal CM risk	Increased CM risk	
Anthropometry												
BMI (kg/m^2)	32.2 (3.3)	32.7 (3.3)	0.058	32.5 (3.3)	32.9 (3.5)	0.098	32.5 (3.2)	32.6 (3.5)	0.939	32.5 (3.3)	32.7 (3.4)	0.242
WC (cm)	107 (10)	108 (9)	0.091	107 (9.19)	109 (8.96)	**0.003**	107 (9)	108 (9)	0.148	107 (10)	108 (9)	0.264
WHR	0.984 (0.080)	0.985 (0.076)	0.764	0.982 (0.076)	0.998 (0.077)	**0.002**	0.980 (0.078)	0.992 (0.073)	**0.006**	0.985 (0.078)	0.985 (0.075)	0.936
WtHR	0.655 (0.056)	0.662 (0.054)	0.064	0.658 (0.053)	0.672 (0.056)	<**0.001**	0.662 (0.054)	0.659 (0.055)	0.444	0.659 (0.054)	0.663 (0.054)	0.201
DXA												
TBF (%)	41.2 (6.4)	40.4 (7.2)	0.094	40.6 (7.0)	40.6 (6.9)	0.962	41.2 (7.0)	39.7 (6.9)	<**0.001**	40.4 (7.0)	40.9 (6.9)	0.167
Trunk fat (g)	20,243 (4046)	20,395 (4452)	0.612	20,195 (4334)	21,001 (4420)	**0.010**	20,336 (4366)	20,397 (4361)	0.813	20,018 (4253)	20,768 (4458)	**0.003**
Android fat (g)	3685 (872)	3713 (933)	0.650	3672 (919)	3841 (909)	**0.010**	3684 (921)	3743 (917)	0.278	3646 (912)	3780 (923)	**0.011**
VAT (g)	2197 (810)	2309 (912)	0.067	2229 (867)	2497 (948)	<**0.001**	2230 (900)	2367 (871)	**0.009**	2251 (893)	2323 (887)	0.159
SAT (g)	1489 (651)	1415 (694)	0.116	1451 (668)	1358 (745)	0.055	1461 (668)	1387 (708)	0.068	1407 (660)	1462 (713)	0.162
Legs fat (g)	9546 (2897)	9091 (3098)	**0.030**	9321 (3024)	8705 (3146)	**0.005**	9448 (3108)	8804 (2939)	<**0.001**	9222 (3097)	9163 (3013)	0.740
Gynoid fat (g)	5031 (1209)	4914 (1384)	0.208	4960 (1344)	4867 (1357)	0.337	5027 (1346)	4807 (1338)	**0.006**	4900 (1335)	4989 (1361)	0.254
Trunk/Legs fat	2.26 (0.62)	2.42 (0.70)	<**0.001**	2.32 (0.65)	2.62 (0.77)	<**0.001**	2.31 (0.68)	2.49 (0.68)	<**0.001**	2.34 (0.67)	2.43 (0.70)	**0.014**
Android/Gynoid fat	0.756 (0.184)	0.786 (0.200)	**0.022**	0.769 (0.194)	0.821 (0.199)	<**0.001**	0.761 (0.196)	0.808 (0.194)	<**0.001**	0.773 (0.197)	0.787 (0.195)	0.213
VAT/Total fat	0.064 (0.022)	0.068 (0.025)	**0.017**	0.066 (0.024)	0.074 (0.026)	<**0.001**	0.065 (0.024)	0.071 (0.024)	<**0.001**	0.067 (0.025)	0.068 (0.024)	0.465
SAT/Total fat	0.042 (0.014)	0.040 (0.015)	0.084	0.041 (0.014)	0.038 (0.017)	**0.004**	0.041 (0.015)	0.040 (0.016)	0.070	0.040 (0.015)	0.041 (0.015)	0.517
VAT/SAT	1.98 (1.64)	2.73 (4.87)	**0.012**	2.29 (3.46)	3.58 (6.73)	<**0.001**	2.33 (4.03)	2.91 (4.83)	**0.023**	2.42 (3.22)	2.72 (5.42)	0.246

BMI – body mass index; CM – cardiometabolic; DXA – dual-energy x-ray absorptiometry; HbA1c – glycated hemoglobin; HDL-C – high-density lipoprotein cholesterol; SAT – subcutaneous adipose tissue; TBF – of total body fat; TG – triglycerides; VAT – visceral adipose tissue; WC – waist circumference; WHR – waist-to-hip ratio; WtHR – waist-to-height ratio. Data are expressed as mean (±SD). Statistical significance determined using one-way analysis of variance. The cut-off threshold to indicate subjects at CM risk were as follows: blood pressure SBP ≥ 130 mmHg and/or DBP ≥ 85 mmHg; HbA1c ≥ 6.5%; TG ≥ 150 mg/dL; HDL-C < 50 (for women) and <40 (for men). In bold, p values < 0.05.

Table 2
Partially-adjusted correlations matrix of the different body adiposity indicators with cardiometabolic risk parameters.

A. Men								
n = 626	SBP (mmHg)	DBP (mmHg)	HbA1c (%)	TyG	TG (mg/dL)	LDL-C (mg/dL)	HDL-C (mg/dL)	TG/HDL-C
Anthropometry								
BMI (kg/m^2)								
WC (cm)			0.085*					
WHR		−0.082*				−0.106**		
WtHR			0.080*					
DXA								
TBF (%)	−0.134**		0.095*					
Trunk fat (g)			0.092*					
Android fat (g)			0.104**					
VAT (g)			**0.161*** **	0.119**				
SAT (g)		−0.101*		−0.081*				−0.079*
Leg fat (g)	−0.139**	−0.091*						
Gynoid fat (g)	−0.096*							
Trunk/Legs fat	0.109**	0.119**		0.123**	0.101*			0.113**
Android/Gynoid fat				0.111**	0.088*			0.095*
VAT/Total fat		0.107**	**0.149*** **	0.136**	0.099*			0.105**
SAT/Total fat		−0.100*	−0.126**	−0.095*				
VAT/SAT		0.105**	0.136**	0.118**	0.083*			0.092*
B. Women								
n = 581	SBP (mmHg)	DBP (mmHg)	HbA1c (%)	TyG	TG (mg/dL)	LDL-C (mg/dL)	HDL-C (mg/dL)	TG/HDL-C
Anthropometry								
BMI (kg/m^2)	0.092*	0.123**						
WC (cm)	0.091*						−0.114**	
WHR		−0.089*	**0.147*** **	0.099*				0.082*
WtHR	0.106*							
DXA								
TBF (%)								
Trunk fat (g)	0.093*	0.108**					−0.117**	
Android fat (g)		0.094*		0.115**			−0.129**	0.097*
VAT (g)		0.082*	0.126**	**0.188*** **	0.142**		**−0.165*** **	**0.176*** **
SAT (g)								
Leg fat (g)			**−0.145*** **	−0.109**	−0.096*			−0.102*
Gynoid fat (g)		0.102*	−0.092*		−0.086*			
Trunk/Legs fat			**0.195*** **	**0.195*** **	0.143**		**−0.172*** **	**0.174*** **
Android/Gynoid fat			**0.206*** **	**0.191*** **	0.140**		−0.143**	**0.166*** **
VAT/Total fat			**0.163*** **	**0.190*** **	**0.151*** **		**−0.145*** **	**0.178*** **
SAT/Total fat								
VAT/SAT			0.100*	0.134**	0.120**		−0.096*	0.137**
C. Men and Women combined								
n = 1207	SBP (mmHg)	DBP (mmHg)	HbA1c (%)	TyG	TG (mg/dL)	LDL-C (mg/dL)	HDL-C (mg/dL)	TG/HDL-C
Anthropometry								
BMI (kg/m^2)	0.061*	0.060*				−0.064*		
WC (cm)		0.063*	0.078**	0.057*		−0.059*		
WHR		−0.085**	0.099**	0.072*	0.059*	−0.076**		
WtHR	0.057*		0.075**			−0.067*		
DXA								
TBF (%)								
Trunk fat (g)			0.069*	0.078**			−0.070*	0.060*
Android fat (g)			0.092**	0.099**	0.059*		−0.065*	0.075**
VAT (g)		0.078**	**0.157*** **	**0.159*** **	**0.111*** **		**−0.101*** **	**0.133*** **
SAT (g)								
Leg fat (g)	−0.065*			−0.065*	−0.063*			−0.072*
Gynoid fat (g)								
Trunk/Legs fat	0.095**	0.061*	**0.118*** **	**0.160*** **	**0.126*** **		**−0.132*** **	**0.153*** **
Android/Gynoid fat			**0.136*** **	**0.160*** **	**0.122*** **		**−0.108*** **	**0.143*** **
VAT/Total fat		0.068*	**0.161*** **	**0.161*** **	**0.119*** **		**−0.107*** **	**0.141*** **
SAT/Total fat		−0.058*	−0.074*					
VAT/SAT		0.066*	**0.130*** **	**0.115*** **	0.085**		−0.083**	**0.107*** **

*p < 0.05; **p < 0.01; ***p < 0.001.
BMI – body mass index; CM – cardiometabolic; DXA – dual-energy x-ray absorptiometry; DBP – diastolic blood pressure; HbA1c – glycated hemoglobin; HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; SAT – subcutaneous adipose tissue; SBP – systolic blood pressure; TBF – of total body fat; TG – triglycerides; TyG – triglycerides and glucose index; VAT – visceral adipose tissue; WC – waist circumference; WHR – waist-to-hip ratio; WtHR – waist-to-height ratio. Values shown are those correlation coefficients (rho) that were statistically significant ($p < 0.05$; Spearman's partial correlation), and those highlighted in bold were those with $p < 0.001$. The model used for analysis was adjusted for recruitment center, age, diabetes prevalence, treatment with antihypertensive (in case of SBP and DBP) and cholesterol lowering (in case of LDL-C) medications. Additionally, the model was adjusted for sex when considering data from men and women as a whole. In bold, those correlations that are statistically significant (p-value < 0.05)

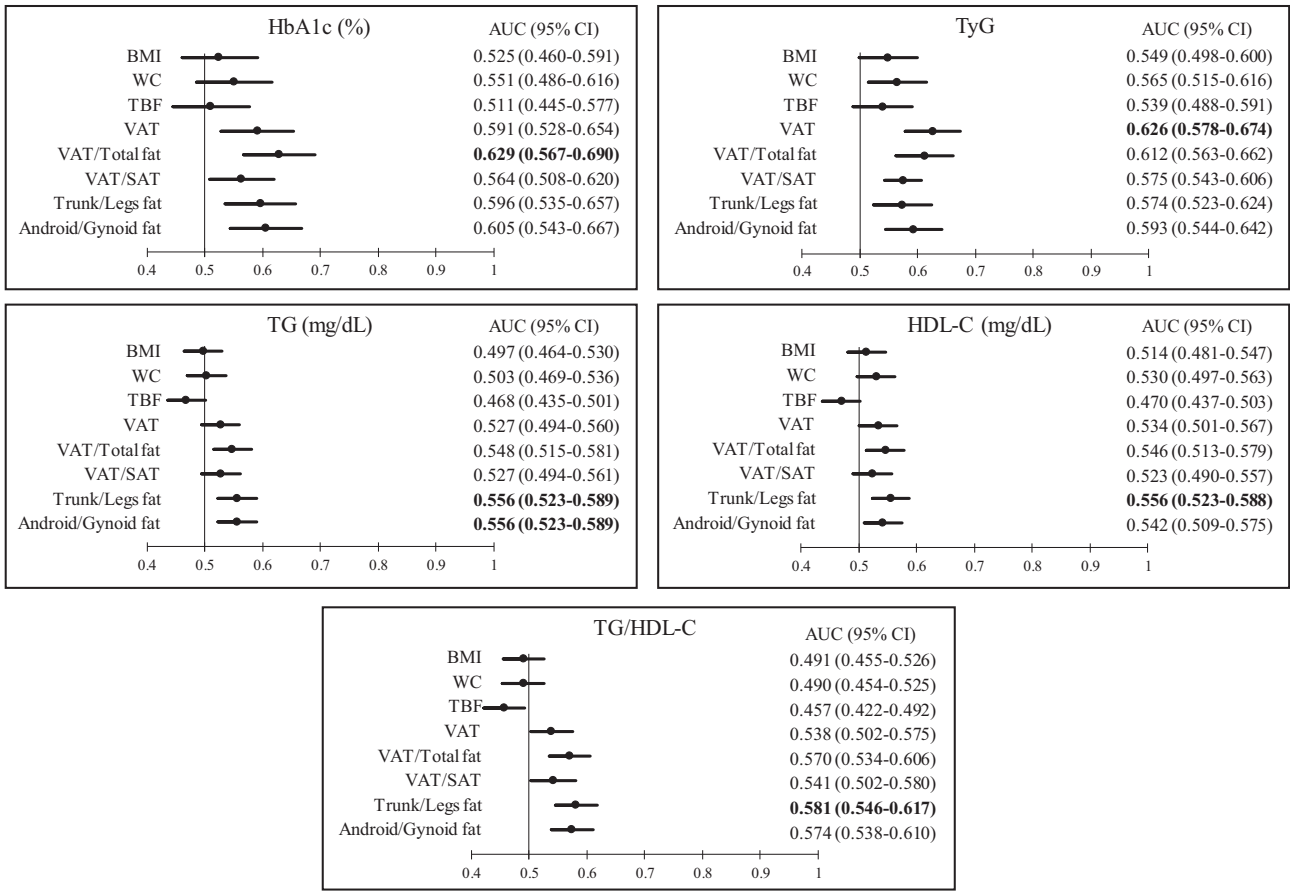

Fig. 1. Adjusted area under the ROC curve analysis for body adiposity indicators and selected cardiometabolic risk parameters (n = 1207). AUC – area under receiver operating characteristic (ROC) curve; BMI – body mass index; CI – confidence interval (CI); CM – cardiometabolic; DXA – dual-energy x-ray absorptiometry; HbA1c – glycated hemoglobin; HDL-C – high-density lipoprotein cholesterol; TBF – of total body fat; TG – triglycerides; TyG – triglycerides and glucose index; VAT – visceral adipose tissue; WC – waist circumference. The AUCs and CIs of different adiposity indicators normalized into z-scores for elevated CM risk parameters in men and women analyzed jointly. The model used for analysis was adjusted for recruitment center, age, diabetes prevalence (HbA1c $\geq$ 6.5, previously diagnosed diabetes, use of antidiabetic medication (insulin, metformin (in case of diagnosed diabetes or HbA1c $\geq$ 6.5) or others), and sex). The highest AUC value for each CM risk parameter is highlighted in bold.

smoking status, alcohol intake, total leisure-time physical activity and adherence to MedDiet), are presented in Supplementary Table 3. In general terms, results of these additional analyses were similar to those reported, and further adjustment for lifestyle variables did not alter the results.

In sensitivity analyses (data not shown), excluding patients with metallic prosthesis or adjusting for time difference between DXA measurements and biochemical and blood pressure determinations did not affect the estimates. Furthermore, we found statistically significant interactions by diabetes status in some of the studied associations (data not shown): for instance, increments in TBF (1 SD) were associated with lower TG levels in non-diabetics ($\beta = -8.67$, $p < 0.05$), but not in diabetics ($\beta = 9.87$, NS) (p for interaction = 0.006); increments in Trunk/Legs fat (1SD) were associated with greater HbA1c in diabetics ($\beta = 0.24$, $p < 0.001$), than in non-diabetics ($\beta = 0.03$, $p < 0.05$) (p for interaction <0.001); increments in VAT/Total fat (1SD) were associated with greater HbA1c in diabetics ($\beta = 0.37$, $p < 0.001$), than in non-diabetics ($\beta = 0.06$, $p < 0.01$) (p for interaction <0.001).

4. Discussion

The optimal body adiposity measures are required for CM disease prevention and control. In this cross-sectional analysis, the ability of a comprehensive set of various adiposity indicators for CM risk assessment was compared. Among them, traditional anthropometric, as well as standard and novel DXA-derived parameters were tested. Drawn from the PREDIMED-Plus trial, the sample of senior subjects with overweight/obesity and adverse metabolic health was used. The present study revealed that DXA regional adiposity measures offer advantages beyond traditional anthropometric and DXA overall adiposity indicators, in terms of CM risk assessment. In particularly, in both sexes, visceral adiposity showed better capacity to stratify individuals at risk for glucose abnormalities, whereas the ratios of central-to-peripheral adiposity worked better for dyslipidemia risk.

Our findings add to existing strong evidence that BMI is neither a biological trait nor it reflects physiological and pathological states, particularly in senior subjects [2,36]. Similarly, TBF, the other commonly used indicator of overall adiposity, albeit precisely and accurately measured by DXA, was limited in evaluating CM risk. Therefore, in line with other authors [16,37], we found in our population that the adiposity distribution was clearly more important than overall adiposity in predicting CM risk. Furthermore, anthropometric surrogates of abdominal obesity, such as WC, WHR or WHtR, albeit better than BMI, were inferior than DXA-derived parameters of adiposity distribution. As reviewed by Kuk and colleagues, it seems that age-related body composition redistribution occurs independently of overall adiposity or WC, thus cannot be detected by simple anthropometric measures alone [19].

Similar conclusions have been already drawn from earlier reports [17,18], although the clinical guidelines have not been updated so far.

An accurate and precise body composition determinations obtained with DXA, may advance science regarding mechanistic role of specific fat depots in health outcomes, and improve clinical assessment allowing identification of specific phenotypes, such as the metabolically healthy obese or metabolically unhealthy lean subjects. However, it is accepted that use of DXA is still not very feasible in public health screening and most clinical trials. Based on the results from this study, we reinforce that in case in which DXA cannot be applied, WC only or in adjunct with its derivates (WtHR or WHR) should be assessed, as a surrogate measure of visceral adiposity. Ultimately, the utility of WHR has gained less appreciation as a risk indicator for CM risk [38]. However, in the current study, we found that in both sexes WHR had a somewhat very considerable utility. The rationale supporting the use of WHR is that it accounts for central and peripheral fat distribution, which in case of senior subjects might serve as the plausible alternative for the indicators of lipodystrophy.

It is well established that visceral adiposity is associated with adverse CM health. The exact mechanisms responsible for this link are still unclear, albeit the induction of chronic low-grade systemic inflammation mediated by macrophage infiltration and secretion of proinflammatory cytokines might be a key clue [39–42]. Due to known detrimental effects of VAT, there is constantly increasing interest in this fat depot as an attractive tool for disease risk diagnosis and target for interventions. Its widespread use as an adiposity indicator is, however, severely hampered by the lack of accessible and reliable methods to quantify VAT. This study adds to the existing body of evidence that the use of automated DXA-CoreScan algorithms is as valuable method for VAT quantification [15–18,43].

We found that VAT mass, expressed in the absolute value and in relation to total fat or SAT mass, was strongly associated with five parameters related to CM risk. In particular, we confirmed the known association between visceral adiposity and atherogenic lipids profile, i.e. TG and HDL-C levels, as well as TG/HDL-C ratio [16,44–46]. On the other hand, it has been postulated that VAT, plays the crucial role in the development of insulin resistance [39,40]. Our results seem to be in line with this theory, as VAT and VAT/Total fat were not only strongly correlated but were also the most robust predictors of elevated HbA1c, and TyG index — a marker associated with insulin resistance [47], as well as early predictor of DM2 and CV event risk [31,48]. Previous studies also reported an adverse association between visceral adiposity and CV and metabolic risk, which were primarily driven by insulin resistance [17,41,49].

Aging has not only been associated with increases in total or abdominal adiposity but also with the progressive loss of peripheral SAT, particularly in the lower body areas [19]. It has been proposed that the lipodystrophy, manifested by reduced ability of SAT to adequately uptake and store circulating free fatty acids (FFA), leads to excessive lipid accumulation in non-subcutaneous fat or in lean mass [19,50]. Therefore, increases in ectopic fat depots (VAT, liver, heart and muscle) might be attributed, at least partly, to an age-related dysregulation of lipid metabolism in SAT [6]. In this regard, current study revealed that DXA-derived ratios reflecting excess of central in relation to peripheral adiposity emerged as more accurate to evaluate CM risk than the crude measures of trunk, android, legs and gynoid fat alone. In particular, Trunk/Legs fat and Android/Gynoid fat were associated with increased CM abnormalities based on long-term glycemic levels (HbA1c), a marker associated with insulin resistance, T2D and CV event risk conditions (TyG index) [31,47,48], as well as atherogenic lipid profile (TG, HDL-C and TG/HDL-C). Among them, both ratios of fatness were most accurate to discriminate those at risk for atherogenic dyslipidemia. Our results are consistent with previous studies in elderly and postmenopausal women, suggesting that centrality indices — trunk/legs and android gynoid fat ratio — are more accurate predictors of glucose abnormalities and dyslipidemia than central measures (trunk or android fat) alone, unrelated to peripheral adiposity [51–53]. Although the clinical implications of our observations are not fully clear, they reinforce the importance of age-related body fat redistribution, which can be almost undetectable through anthropometry.

Regarding atherogenic lipid profile, most of the associations between adiposity indicators and CM risk were found in relation to TG, HDL-C and TG/HDL-C ratio. In case of LDL-C, there was a small inverse correlation with anthropometric indicators (e.g. WHR) due to chance finding or through the proposal that factors other than obesity/visceral adiposity are involved in the age-related increase of plasma LDL-C levels [54].

Due to the sexual dimorphism in body composition [19,35], the analyses were performed a priori separately for men and women. However, given that after menopause the pattern of fat accumulation in women mirrors that of men [19,35], we found little sex differences in our study. Particularly, the associations between indicators of visceral adiposity and markers of dyslipidemia, as well as between lipodystrophy indicators and the CM risk factors were, to some extent, more pronounced in women than in men. The reason for that is uncertain, but might be attributed to the hepatic delivery of FFA derived from VAT lipolysis [55] and accumulation of peripheral SAT stores over early adulthood [19,35], which was found to be greater in women than in men.

We recognize several strengths and limitations of our study. A marked strength of the present study was the use of large and homogenous sample of men and women within a narrow BMI, TBF and age ranges. Unlike previous studies, we examined wider spectrum of adiposity indicators using anthropometry and DXA, including a variety of upper and lower fat depots. A comprehensive set of parameters related to CM risk, was also addressed. Moreover, measurements of adiposity and CM features were based on physical and laboratory examinations performed with use of standardized protocols, in order to minimize the measurement errors. The amount of VAT was not calculated with use of predictive equations, but determined based on an automated algorithm from the DXA manufacturer, providing valid estimates of this fat depot. We also compared the magnitude of CM risk using standardized z-scores of different adiposity indicators quantified using anthropometry and DXA, thus enabling direct comparisons of risk estimates. Furthermore, in contrast to other studies, the analyses were controlled for the treatment with medications (antihypertensive, cholesterol lowering and antidiabetic), which might influence biochemical and blood pressure results. In addition, the analyses were also adjusted for other important possible covariables, including age, diabetes prevalence, and factors related to healthy lifestyle, as smoking status, alcohol intake, physical activity level and adherence to MedDiet. Finally, sensitivity analyses suggested that the obtained results are not affected by time difference between DXA and CM-related parameters determinations or possession of metallic prosthesis.

The main limitation of this study was it cross-sectional design, which restricts inference regarding causality of the associations found. The selection criteria of the study cohort, including elderly subjects with overweight/obesity and MetS, limits generalization of findings to other populations, as younger, leaner or healthier subjects. Moreover, the health conditions of study participants were likely correlated with the outcome. However, the prevalence of described health conditions, which increases with progressing age,

is relatively common nowadays. Furthermore, the correlation coefficients obtained in our analysis where somehow modest, albeit the magnitude and direction of our findings were consistent with previously reported literature [17,18,37,56,57]. Finally, the study was limited to single-race (Caucasians), hence, the associations found may not be applicable to other ethnic/racial groups. Since, the quantity of fat accumulation in different depots might vary in specific ethnic groups, it would be of interest to replicate our findings in diverse populations.

In conclusion, results from this cross-sectional analysis contribute to the accumulating body of evidence that DXA measures and regional adiposity are stronger predictors of CM risk than anthropometry and overall adiposity. Particularly, visceral adiposity measured with DXA-CoreScan was associated with indicators of glucose abnormalities and T2D and the two DXA-derived ratios of central-to-peripheral adiposity, as Trunk/Legs fat and Android/Gynoid fat, were associated with atherogenic lipid profile and heart health. Future studies should be performed to expand these findings in terms of clinical utility, and to explore mechanistic link between specific fat depots and CM disease development. As a final remark, results from this study indicate that BMI and TBF should not be relied on in clinical practice for CM risk identification in elderly subjects. In case in which DXA cannot be applied, the use of WC and its derivates, as WHR or WtHR, is recommended for the identification of elevated CM risk in this particular group.

Statement of authorship

J.K., I.A., JA.M., and D.R., conceived the study, analyzed the data, and wrote the article. J.K., I.A., A.M.G., N.B., A.C., M.A.Z., R.S., J.Vi., E.T., A.D.-L., M.F., R.C., J.Ve., P.B.-C., V.M., A.G., J.S.-S., JA.M, and D.R designed and conducted the project, and obtained the data. All authors revised the manuscript for important intellectual content and read and approved the final manuscript. J.K. and D.R. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of interest

All authors declare they have no conflict of interest relevant to the content of this article.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clnu.2018.07.005.

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