Nutrition, Metabolism and Cardiovascular Diseases xxx (xxxx) xxx

Contents lists available at ScienceDirect

Nutrition, Metabolism and Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

Abdominal obesity and cardiometabolic risk markers: A comparative analysis of waist circumference, dual-energy X-ray absorptiometry, and magnetic resonance imaging techniques

Giulianna Regeni Ruano [a], Guilherme Augusto Nogueira [b], Prince Dadson [c], Sandra R.G. Ferreira [d], Marcelo Tatit Sapienza [e], Licio A. Velloso [b], Milena Monfort-Pires [b,c,1,*]

[a] Department of Nutrition, School of Public Health - University of São Paulo, São Paulo, SP, Brazil
[b] Laboratory of Cell Signaling, Obesity and Comorbidities Research Center, State University of Campinas (UNICAMP), Campinas, São Paulo, Brazil
[c] Turku PET Centre, University of Turku, Turku, Finland
[d] Department of Epidemiology, School of Public Health - University of São Paulo, São Paulo, SP, Brazil
[e] Division of Nuclear Medicine, Department of Radiology and Oncology, Medical School of University of São Paulo (FMUSP), São Paulo, Brazil

ARTICLE INFO

Handling Editor: Dr. A. Siani

Keywords:
Abdominal obesity
Waist circumference
DXA
MRI
Cardiometabolic risk markers
ROC analysis

ABSTRACT

Background and aims: This study compares three methods to determine central adiposity (waist circumference –WC - and visceral adipose tissue – VAT - estimated by dual-energy x-ray absorptiometry – DXA, and by magnetic resonance imaging - MRI) in their ability to predict increases in cardiometabolic risk (CMR) markers in young individuals. We examined their associations with CMR in 47 men and women aged 25–40.

Methods and results: VAT mass was assessed using DXA and MRI. Blood samples were analyzed for CMR markers. Associations between central adiposity measurements and CMR factors were analyzed using Spearman's correlation coefficient, and the ability of these three central adiposity measurements to detect increased CMR was compared using receiver operating characteristic (ROC) curves. Similar to what was observed for the MRI-DXA and VAT-DXA, WC showed strong correlations with LDL-c and triglycerides (TG) and an inverse correlation with HDL-c (rho = −0.657 MRI, rho = −0.628 DXA, and rho = −0.604 WC, $p < 0.01$). On the other hand, only MRI-VAT and WC were associated with insulin and HOMA-IR (rho = 0.341 MRI and rho = 0.421 WC, $p < 0.01$). Central adiposity measurements were negatively associated with cold-induced ^{18}F-FDG uptake in subcutaneous adipose tissue and positively associated with VAT TG content. No significant differences were observed when comparing the three central adiposity measurements in ROC curve analysis, and all measurements could predict increases in CMR markers and the combined CMR index.

Conclusions: This study reinforces the importance of using WC to assess increases in CMR markers among young adults. Given its practicality and efficacy, WC should be recommended in health centers to assess CMR risk.

1. Introduction

There is undisputed evidence that fat accumulation, especially in the visceral region, is directly associated with high cardiometabolic risk (CMR) [1,2]. This is true not only for subjects with obesity but also for lean and overweight individuals, as even in these groups, increased abdominal adiposity is associated with higher insulin resistance and subclinical inflammation, which are important determinants of increased risk for cardiovascular events [1–4].

Several studies have shown that despite the structural, metabolic, and functional differences of visceral (VAT) and subcutaneous (SAT) adipose tissues, both can contribute to obesity [5–7]. Nevertheless, it has been evidenced that intra-abdominal fat accumulation has a more significant impact on metabolic and cardiovascular disease (CVD) risk than SAT, which is, in part, but not solely, due to its greater capacity to produce inflammatory cytokines [2,8]. It has been shown, for example,

* Corresponding author. The Laboratory of Cell Signaling belongs to the National Institute of Science and Technology, Neuroimmunomodulation, Brazil.
E-mail address: mmopir@utu.fi (M. Monfort-Pires).
[1] Lead Contact.

https://doi.org/10.1016/j.numecd.2024.103801
Received 5 March 2024; Received in revised form 7 November 2024; Accepted 19 November 2024
Available online 30 November 2024

that SAT has clearly defined deep and superficial layers with different metabolic properties [9]. Research suggests that the deep layers are more metabolically active and are strongly linked to metabolic complications, particularly insulin resistance and type 2 diabetes mellitus (T2DM) [1,5], being implicated in various cardiometabolic outcomes due to its cytokine-releasing property and its physical proximity to the liver [4,8,10].

Most studies and guidelines employ the body mass index (BMI) as a standard to define levels of overweight and obesity. However, BMI does not measure fat content or directly assess body fat distribution [11–15], which may hinder its ability to predict cardiometabolic outcomes. Furthermore, the gradual decline in muscle mass with age can further affect the validity and interpretability of BMI as a measure of adiposity [16]. Conversely, waist circumference measurements (WC) exhibit a stronger correlation with the mass of intra-abdominal adipose tissue, which can also be assessed with more sophisticated techniques such as computed tomography (CT) or estimated using dual-energy X-ray absorptiometry (DXA) [17–19].

Even though WC is the most commonly used method for assessing central adiposity due to its simplicity, low cost, and reproducibility [18,20,21], some studies have shown limitations in using this measurement as a predictor of VAT volume, mainly because of its inability to differentiate between intra-abdominal and SAT [7,9,22]. In this context, other techniques, such as MRI and CT, are often considered the standards for evaluating body tissue compartments [23], with DXA showing similar results [24,25]. Indeed, MRI can be used to estimate visceral fat with good accuracy and has been recommended as essential for evaluating abdominal adiposity in clinical research [24,26]. However, both methods still present high costs for epidemiological research, and clinical studies have increasingly used them to produce more accurate data concerning visceral obesity.

The early detection of CMR is essential to prevent the development of CVD in later life, and understanding how central adiposity measurements are associated with risk markers among young and healthy individuals is important to stimulate public policies. The incidence of cardiometabolic diseases among young individuals (<50 years) has increased in the last decades [1,27], mainly due to lifestyle changes. Using data from the Framingham Heart Study, Lloyed-Jones et al. [28] showed that having no risk factors at the age of 50 was associated with a low lifetime risk for CVD and longer survival. In contrast, a Mendelian randomization analysis study observed an adverse effect of increased adiposity with multiple CMR markers among young adults without obesity [29]. These findings indicate that assessing CVD risk markers in young adults, even within the normal BMI range, is essential to prevent the burden of obesity and its comorbidities in later life. Simple measurements, such as WC, could help identify those individuals at higher risk at younger ages.

With these concepts in mind, the present study aimed to compare the ability of central adiposity measurements (WC, DXA-VAT, and MRI-VAT) to detect increased CMR in a group of healthy young adults. Furthermore, the study aimed to determine the association between these measurements with classical and new CMR markers, such as VAT and SAT ^{18}F-FDG uptake, and the content of triglycerides of VAT, SAT, peri-renal fat depot, and liver.

2. Methods

2.1. Design of the study

This is a cross-sectional analysis of a cohort included in a clinical trial that evaluated the effect of monounsaturated fatty acid consumption on brown adipose tissue activity in lean and overweight adults [30]. Since the main study aimed at investigating the brown adipose tissue, all participants underwent 2 h of mild cold exposure before the PET/MRI image acquisition.

2.2. Sample

The sample included 15 individuals with overweight or obesity (BMI $\geq$30 and $<$ 35 kg/m^2 or BMI $\geq$25 with increased WC) and 32 lean individuals (BMI $<$25.0 kg/m^2), totaling 47 participants. They were recruited through print and electronic media advertisements. Further details regarding participant selection are published elsewhere [31].

A sample size was calculated using repeated-measures ANOVA to compare three abdominal obesity estimation tools within the same participants. Based on a desired power of 80 % and a significance level of 0.05, with an estimated moderate effect size in the overall cardiometabolic risk factor (Cohen's f = 0.25), 48 participants are required. This approach allows each participant to serve as their control, thereby reducing variability and enhancing statistical power.

The inclusion criteria for the study were: individuals of both sexes, aged 25–40 years; for the overweight/obesity group, the criteria were: BMI $\geq$30 and $<$ 35 kg/m^2, or a BMI $\geq$25 kg/m^2 with increased WC (greater than 80 cm for women and 90 cm for men); for the lean group, individuals with BMI $<$25 kg/m^2 were considered eligible. The exclusion criteria for both groups are described in the supplementary file.

2.3. Clinical parameters

All subjects were submitted to anthropometric measurements (weight, height, WC), body composition by DXA, and VAT assessment by magnetic resonance imaging (MRI).

Weight measurements were obtained using a digital Toledo® scale, and participants were wearing lightweight clothing and no shoes (recorded to the nearest decimal fraction). Height was measured using a fixed stadiometer (recorded to the nearest 0.1 cm). WC was measured at the midpoint between the lower edge of the last rib and the upper edge of the iliac crest (to the nearest 0.1 cm), with two measurements taken and the average used.

PET/MRI data were acquired using a General Electric® Medical Systems (3T) MRI at the Nuclear Medicine Department of the Clinics Hospital of the University of Sao Paulo. All images were analyzed using Carimas software v.2.10 (Turku PET Centre, Turku, Finland). Volumes of interest (VOI) were outlined using fat fraction and Dicon images for anatomical reference. A minimum of 40 % triglyceride content in the tissue was considered for VAT [31]. The analysis covered the region between L3-L4 and L2-L3 vertebrae (VAT-MRI), applying a 40 % triglyceride content filter. Manual fat checking ensured accurate marking, excluding areas like intestines. VAT volume was converted to mass, assuming a fat density of 0.9196 [32]. The content of triglycerides (TG) in subcutaneous, visceral, and peri-renal adipose tissues (AT) was calculated using fat fraction images. For subcutaneous AT, the VOI was drawn next to the umbilical mark, whereas for the visceral AT, the area between L2 and L3 was used as a reference for the VOI. The VOI for peri-renal fat was drawn on both sides of the fat pad surrounding the kidneys. A VOI was drawn in the lower part of the left lobe for liver analysis, avoiding blood vessels. The ^{18}F-FDG PET/MRI protocol used to calculate the subcutaneous and visceral adipose tissue's glucose uptake values (SUVs) is described elsewhere [30] and in short in the supplementary file.

DXA data were obtained using the GE Lunar iDXA® equipment (Madison, WI, USA) at the School of Public Health - University of Sao Paulo. Correction of points (regions of interest - ROIs) was performed, and the equipment underwent all necessary calibrations before and during data collection. VAT values were automatically estimated using CoreScan software (EnCore version 15.0), with measurements conducted by trained professionals.

Resting blood pressure was assessed with an Omron automatic oscillometer device (Health Care, USA), and the participant was placed in a supine rest position after a 5-minute rest period. Blood samples were obtained after an 8-hour fast. Glucose levels were determined with a glucometer (Accu Check Active device, Roche). Lipid profiles were

analyzed through colorimetric enzymatic methods, with LDL calculated by the difference.

Insulin levels were analyzed using enzyme-linked immunosorbent assay (ELISA, R&D Systems), and HOMA-IR was calculated according to Matthews et al. [33]. Leptin, monocyte chemoattractant protein-1 (MCP-1), and interleukin-6 (IL-6) were measured by ELISA assays (R&D Systems, Minneapolis, MN, USA). The sensitivity and assay ranges of the ELISA kits are described in the supplementary file.

Since the study's primary aims included evaluating brown adipose tissue activity, any medication affecting body weight, lipid, or glucose homeostasis was considered an exclusion criterion. Volunteers were asked on the first day about the use of other medications (oral contraceptives, painkillers, and anti-inflammatories). Any medications or health conditions affecting the study's aims were considered exclusion criteria.

2.4. Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics 28.0.1, and MedCalc® software (version 23.0.6) was used to compare ROC AUCs (using DeLong approach). Data are presented as mean and standard deviation or as median and interquartile range for variables without normal distribution. For comparisons between groups (men versus women), an independent samples *t*-test or non-parametric equivalent (Mann-Whitney) was used. For correlation analyses, the Spearman correlation coefficient was used. A false discovery rate (FDR) test for multiple comparisons was applied. To compare the ability of the three central adiposity measurements in their association with CMR markers, a receiver operating characteristic (ROC) analysis was employed, and the area under the curve (AUC) for each variable was compared.

2.4.1. ROC analysis

The equivalence test, using a margin of ±0.05 between the CI of the AUCs, was employed to compare the three central adiposity measurements. Differences higher than ±0.05 between curves were considered significant.

No ROC analysis was conducted for fasting glucose as normal fasting glucose was one of the inclusion criteria for the study, and there is no clear evidence of lower CMR for different glucose values below 99 mg/dL [34]. For systolic and diastolic blood pressure, as well as for triglycerides, more than 95 % of the volunteers presented normal values according to the International Diabetes Federation (IDF) criteria and current recommendations from international authorities (135/85 mmHg and 150 mg/dL, respectively) [11]. Therefore, 120 mmHg and 80 mmHg were considered cutoff values for systolic and diastolic blood pressure (respectively), as previously described [34]. The median of the total sample (83 mg/dL) was employed for triglycerides. Notably, the TG median values were similar to a cutoff previously reported [35]. As reference values differ among studies, the median value was used as a cutoff for leptin, but men and women were considered separately. Variables without any literature reference, such as glucose uptake (in SUVs) and triglyceride content in different tissues, were analyzed according to median values. For total cholesterol, LDL, and HDL, the IDF criteria were employed (<200 mg/dl, <150 mg/dL, and >40 mg/dL for men and >50 mg/dl for women, respectively) [11]. Lastly, for insulin (5.35 mU/L) [36,37], HOMA-IR (1.22) [36,37], MCP-1 (157 pg/ml) [38], and IL-6 (5.186 pg/ml) [39] cutoff values were defined based on previous studies.

Since there are no validated tools to identify increased CMR in young adults without clear CMR, a combined CMR variable using systolic and diastolic blood pressure, LDL-cholesterol, HDL-cholesterol, triglycerides, and HOMA-IR was created. The elevated risks for each variable were combined into a single index to understand the ability of measurements to predict CMR according to the primary CMR markers available in our study. The individuals were then classified according to the number of altered risk factors (≤2 or ≥3). Because only 25 % of the sample had one or fewer altered CMR markers, classifying the participants with no risk would reduce the sample size and the power of the analysis. On the other hand, almost half of the sample presented three or more increased risk markers. Therefore, a cutoff value of two was used, as reported in other combined indexes. In addition, we checked the associations between our CMR and the Framingham risk score, which has been used as a predictor for increased risk of cardiovascular diseases [40]. We observed a correlation of 0.500 ($p < 0.01$), suggesting that our selection of CMR could be used as a proxy of CMR in our sample. A p-value of less than 0.01 (adjusted α for the number of tests for three ROC curves) was considered significant.

2.5. Ethical considerations

The study was approved by the Research Ethics Committees of the Faculty of Medical Sciences of the State University of Campinas, the Faculty of Medicine of the University of São Paulo, and the Faculty of Public Health of the University of São Paulo. The CAEE number is 60698716.1.0000.5404.

3. Results

This study included 47 individuals; 15 were overweight or with obesity (BMI ≥25 kg/m^2 with high WC or BMI>30 kg/m^2), and 32 were lean (BMI <25 kg/m^2, data not shown). When stratified according to the CRM risk combined variable, 26 individuals were classified as low risk, whereas 18 were classified as high risk. Three participants had missing data for cholesterol and were not included in any group. Still, they had data for other markers and were included in the analysis of specific markers. The majority were women (59.6%), and approximately 35% of participants reported continuous use of medication, primarily painkillers and oral contraceptives.

Table 1 displays the clinical data of the subjects according to CMR groups. There was no significant age difference between low and high-CMR individuals (31.5, IQR 28–34.3 versus 35.0, IQR 27.8–39, $p = 0.12$) or number of women in each group ($p = 0.76$). However, as expected, we observed significant differences in anthropometric variables such as weight (63 kg, IQR: 55.9–72.8 versus 77.3 kg, IQR 59.6–93.5, $p < 0.01$), BMI, and WC (76.9 cm, IQR: 72.3–86.7 cm in low-CMR versus 92.5 cm, IQR: 75.9–100.7 cm in individuals with high-CMR; all with $p < 0.01$). As for the clinical data, there were differences between the groups in LDL-cholesterol (100.5 mg/dl, IQR: 88.0–125.5 mg/dL in low-CMR versus 128.4 mg/dl, IQR: 100.0–151.0, in the high CMR group, $p < 0.01$), HDL-cholesterol (58.5 versus 43.9 mg/dl: $p = 0.04$), and triglyceride levels (63.5, IQR: 56.8–85.3 mg/dl versus 112.5 mg/dl, IQR: 88.8–147.0, $p < 0.01$). Similar findings were detected for glucose (77 mg/dl versus 84.5 mg/dl, $p = 0.04$), but not insulin ($p = 0.15$), and HOMA-IR ($p = 0.07$). As expected, leptin concentrations (57.3 pg/ml, IQR: 31.7–81.4 in low CMR versus 343.7 pg/ml, IQR: 57.5–343.7 in high-CMR group, $p < 0.01$) differed between groups. Conversely, between groups, MCP-1 and interleukin-6 (0.51 and 0.91, respectively) were similar. In addition, systolic blood pressure (107.5 versus 120 mmHg, $p = 0.01$), but not diastolic blood pressure, differed between the groups.

Concerning PET/CT data, subcutaneous (0.27, IQR: 0.19–0.32 in the low-CMR group versus 0.14, IQR: 0.11–0.27 in the high-CMR group, $p < 0.01$) but not visceral adipose tissue SUV (0.52, IQR: 0.36–0.67 versus 0.42 IQR: 0.33–0.62, $p = 0.41$) was higher in the low-CMR group, whereas the content of triglycerides in subcutaneous and peri-renal, but not visceral (80.8 %, IQR: 71.5–8.1 % versus 85.0 %, IQR: 85.8–93.9 %), adipose tissues were higher among those with higher CMR ($p < 0.01$ for all).

Table 2 shows DXA body composition data for the low and high-CMR groups. As expected, there were differences between them in most body composition variables, with the exception being the fat-free mass in

Table 1
Characteristics of the sample according to CMR (low- and high-CMR) (n = 47).

	Low CMR (n = 26)	High CMR (n = 18)	Total sample (n = 47)[a]	p-value
Sex (number of women)	16	10	28	0.76
Age (years)	31.5 (28–34.3)	35 (27.8–39)	32.0 (28.0–37.0)	0.12
Body weight (kg)	63 (55.9–72.8)	77.3 (59.6–93.5)	70.7 (56.7–80.2)	0.04
Body mass index (kg/m2)	22 (20.1–24.3)	27 (21.9–31.8)	23.1 (20.8–28.1)	0.01
Waist circumference (cm)	76.9 (72.3–86.7)	92.5 (75.9–100.7)	81.3 (73.1–95.9)	0.01
Systolic blood pressure (mmHg)#	108 (103.5–117)	117.5 (104.3–127.5)	113.0 (104.0–120.0)	0.01
Diastolic blood pressure (mmHg)#	62 (60.5–69)	69.5 (64.3–81.3)	66.0 (61.0–76.0)	0.07
Fasting glucose (mg/dl)	77 (65.5–83)	84.5 (75.8–86.3)	77 (69.8–86.0)	0.047
Insulin (μU/L)	3.8 (2.9–5.2)	5.0 (3.2–7.4)	4.1 (3.0–5.41)	0.15
HOMA-IR	0.8 (0.5–1)	0.9 (0.6–1.5)	0.82 (0.55–1.09)	0.07
Total cholesterol (mg/dl)	177.5 (162.8–195.5)	203 (185.8–223.8)	185.5 (172.8–213.3)	<0.01
LDL cholesterol (mg/dl)	100.5 (88–125.5)	128.4 (110–151)	111.5 (94.6–135.0)	<0.01
HDL cholesterol (mg/dl)	58.5 (50.7–63.7)	43.9 (39.3–57.1)	55.0 (42.7–62.0)	0.04
Triglycerides (mg/dl)	63.5 (56.8–85.3)	112.5 (88.8–147)	83.0 (59.3–115.5)	<0.01
Leptin (pg/ml)#	57.3 (31.7–81.4)	119.5 (57.5–343.7)	76.5 (42.1–125.4)	<0.01
MCP-1 (pg/ml)#	224.8 (192.8–267.4)	229.9 (196.1–303.6)	229.0 (196.4–286.8)	0.51
Interleukin-6 (pg/ml)#	7.1 (6.47–7.96)	7.21 (4.72–8.18)	7.2 (6.44–8.15)	0.91
Subcutaneous AT (SUV)	0.27 (0.19–0.32)	0.14 (0.11–0.27)	0.23 (0.14–0.31)	<0.01
Visceral AT (SUV)	0.52 (0.36–0.67)	0.42 (0.33–0.62)	0.48 (0.36–0.65)	0.41
Subcutaneous AT %TAG	83.5 (75.4–88.8)	90.2 (82–91.8)	84.4 (77.2–91.0)	0.04
Visceral AT % TAG	80.8 (71.5–88.1)	85.0 (81.9–90.2)	83.0 (76.3–89.9)	0.11
Liver % TAG	3.12 (2.01–7.91)	4.69 (2.35–7.35)	4.1 (2.1–7.4)	0.54
Peri-renal % TAG	75.3 (70.5–79.2)	86.1 (79.6–90.3)	78.9 (71.2–86.4)	<0.01

Mann Whitney rank test.
Median and interquartile range.
[&]non-parametric distribution/#n ≥ 40.
[a] Three participants had missing data for cholesterol and were not included in the CMR groups.

Table 2
Body composition variables according to CMR (low- and high-CMR).

	Low CMR (n = 26)	High CMR (n = 18)	Total sample (n = 47)	p-value
Total fat mass (kg)	16.67 (14.99–19.9)	23.55 (18.63–33.72)	19.2 (16.0–27.6)	<0.01
Total fat mass (%)	28.1 (25.23–31.05)	34.4 (27.98–41.23)	30.8 (26.0–35.0)	<0.01
Fat mass index (mg/m^2)	6.04 (5.36–6.89)	8.55 (6.28–12.42)	6.53 (5.7–8.7)	<0.01
Android/ gynoid ratio	0.89 (0.66–1.17)	1.08 (0.95–1.24)	1.02 (0.79–1.18)	0.045
DXA-VAT (g)	177.5 (58.75–422.25)	632.5 (243–1389.5)	276 (85.0–718.0)	<0.01
Total lean mass (Kg)	41.05 (36.25–51.15)	44.04 (37–53.24)	43.7 (37.0–51.6)	0.45
Arm fat (%)	29.1 (21.1–32.68)	35.95 (24.65–41.03)	29.5 (25.8–32.8)	0.10
Arm fat (kg)	1.75 (1.46–2.23)	2.26 (1.97–3.56)	2.0 (1.67–2.66)	<0.01
Arm fat-free mass (kg)	3.99 (3.53–6)	4.72 (3.35–6.97)	4.39 (3.56–6.30)	0.46
Leg fat (%)	32.35 (24.53–35.53)	35.2 (26.2–41.8)	32.9 (25.6–36.4)	0.14
Leg fat (kg)	6.74 (5.83–7.68)	7.91 (6.51–11.15)	7.0 (6.11–8.83)	0.04
Leg fat-free mass (kg)	14.84 (12.22–17.44)	16.18 (12.72–19.23)	15.62 (12.42–18.65)	0.47
Trunk fat (%)	27.55 (22.68–31.73)	36.25 (29.53–43.63)	30.30 (26.60–37.70)	<0.01
Trunk fat (kg)	7.82 (6.07–9.64)	13.64 (8.25–18.86)	8.76 (6.89–14.92)	<0.01
Trunk fat-free mass (kg)	20.01 (16.99–23.71)	20.43 (18.59–24.83)	20.41 (17.92–24.52)	0.567
MRI-VAT (L3-L4 mass, g)	22.64 (16.09–58.8)	75.9 (36.06–131.99)	57.60 (19.28–91.87)	<0.01
MRI-VAT (L2-L3 mass, g)	26.00 (15.16–47.32)	75.42 (28.06–128.70)	55.62 (17.52–87.17)	<0.01

*Three participants had missing data for cholesterol and were not included in the CMR groups.
Mann Whitney rank test.
Median and interquartile range.

arms, trunk, and legs, as well as leg fat percentage (32.3%, IQR: 24.53–35.53 versus 35.2%, IQR: 26.2–41.8, p = 0.14). When assessing the android/gynoid ratio and the fat mass index (which factors in height along with fat percentage), the fat distribution between the groups was significant (p = 0.04). Similar results were observed when analyzing the VAT mass between MRI-VAT (L2-L3 mass 26.0g, IQR:15.16–47.32 in low-CMR versus 75.42g, IQR: 28.06–128.70 in the high-CMR group, p < 0.01) and DXA-VAT (177.5g, IQR: 58.75–422.85g in lean versus 632g, IQR: 243.0–1389.5g, p < 0.01)(Table 2).

Fig. 1 depicts the correlation heat map of associations between distinct adiposity measurements and clinical parameters, with markers of central obesity obtained using different instruments: WC, VAT from DXA, and VAT from MRI. Our analyses reveal that all whole-body adiposity measurements exhibit robust and consistent correlations with WC, DXA-VAT, and MRI-VAT (calculated from L2-L3 and L3-L4 fat mass), except leg fat percentage and relative fat mass. As expected, the three central adiposity variables exhibited strong associations with trunk fat. Moreover, significant correlations existed among the central adiposity measurements themselves. Interestingly, the three central adiposity variables were also correlated with fat-free mass, which remained statistically significant after FDR correction (p < 0.05).

Regarding clinical variables, central adiposity measurements were correlated with systolic blood pressure but not diastolic, LDL cholesterol, and triglycerides, whereas HDL showed inverse correlations with all three variables. Conversely, WC was the only central adiposity measurement associated with all other clinical variables (fasting insulin, HOMA-IR, and total cholesterol). The DXA-derived VAT and MRI-derived VAT were not associated with all glucose metabolism variables. Moreover, leptin concentrations were positively correlated only to DXA-derived VAT, while MCP-1 was associated with WC and MRI-VAT but not with DXA-VAT. IL-6, on the other hand, was associated with DXA-VAT and MRI-VAT but not with waist circumference. However, all these associations were lost after FDR's correction (Fig. 1).

As the glucose uptake by adipose tissue (in SUVs) was shown to be inversely correlated to obesity and CMR in previous studies, we sought to analyze how the central adiposity markers associated with cold-induced glucose uptake (in SUVs) calculated from PET data in both abdominal subcutaneous adipose (SAT) tissue and visceral adipose tissue (VAT). Indeed, all three measurements of central obesity were inversely associated with subcutaneous and visceral SUV. Moreover, we analyzed the associations between WC, DXA-VAT, and MRI-VAT with the content of triglycerides of SAT and VAT, as well as the liver fat

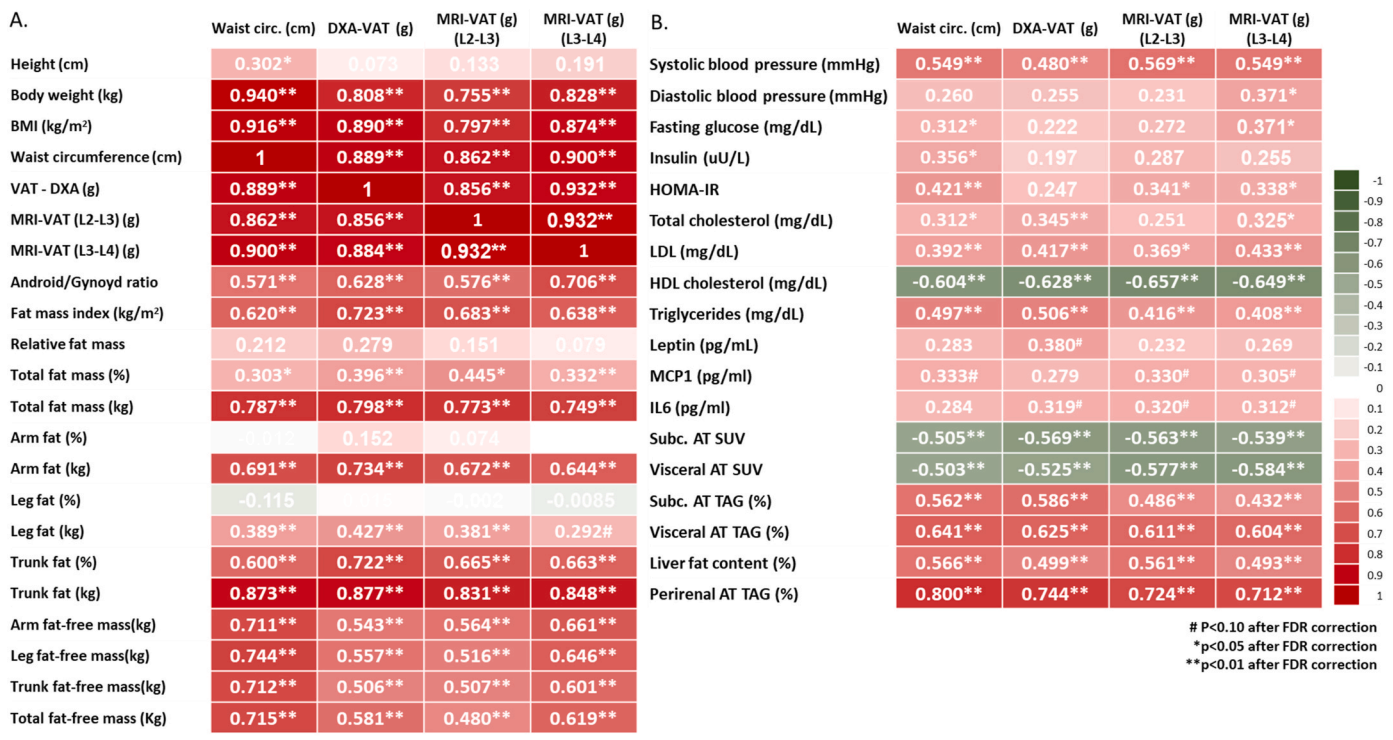

Fig. 1. Heat map of Spearman's correlations between WC measurements, DXA-VAT, and MRI-VAT with cardiometabolic risk markers and adiposity measurements. Fig. 1 **legend:** Spearman's correlation between waist circumference measurements, DXA-VAT, and MRI-VAT (from L2-L3 and L3-L4 areas) with body composition variables (A) and cardiometabolic risk markers (B).

content and peri-renal fat depots. As expected, all central adiposity measurements were directly associated with the fat content in these depots (Fig. 1), even after FDR correction.

Next, we employed a ROC curve analysis to compare the ability of the three different central adiposity measurements to identify increases in CMR markers. We aimed to understand whether WC could be equally or better associated with these parameters (Fig. 2, Supplementary Fig. 1, Table 3). When ROC analyses were performed, we observed that all three central adiposity measurements presented good models to predict increases in most CMR markers, including the combined CMR variable. Increases in WC, VAT-DXA, and MRI-DXA predicted higher systolic, but not diastolic blood pressure, insulin, HOMA-IR, LDL-cholesterol, triglycerides, and leptin (Fig. 2, Supplementary Fig. 1, and Table 3). Moreover, they could predict lower HDL-cholesterol (<40 mg/dl for men and <50 mg/dL for women). Only for total cholesterol, WC did not predict its higher concentrations (Supplementary Fig. 1C, Table 3). Still, no differences between AUCs were detected when comparing the equivalence margin for these variables (equivalence margin within 0.05 predefined margin for all variables, Supplementary Table 1). On the other hand, WC showed a non-significant higher AUC for insulin and HOMA-IR compared to DXA-VAT and MRI-VAT, confirming the results of the correlation analyses (Table 3, Fig. 2C and Suppl. Fig. 1B). Although the AUCs were higher for WC, the equivalence margins analysis showed no statistical differences between measurements (Supplementary Table 1). Notably, when the overall CMR was analyzed, all three models showed similar AUCs (Fig. 2A–Table 3, $p > 0.05$). Significantly, all AUCs fell within the 0.05 interval of the predefined equivalence margin (0.037 CI: −0.04 to 0.12, for WC versus DXA-VAT, 0.022, CI -0.044 to 0.088, for WC versus MRI-VAT and 0.01, CI: −0.055 to 0.085 for DXA-VAT versus MRI-VAT). The WC cutoff for the combined CMR was 96.5 cm, whereas DXA-VAT was 261g and DXA-MRI 51.9g (Fig. 2A), suggesting that these values could be used as a reference for increased risk in this sample.

The three central adiposity measurements did not provide a good model to predict increased levels of IL-6 and MCP-1 (Suppl. Figs. 1D and 1E, and Table 3). Conversely, DXA-VAT, MRI-VAT, and WC showed elevated AUCs for glucose uptake in both VAT and SAT, confirming their ability to identify changes in this marker (Table 3 and Fig. 2H and I). The three indexes showed similar results when comparing AUCs (Fig. 2 and Table 3, within the predefined equivalence margin). Similarly, all three measurements had good prediction models for high content of TG in VAT (Table 3 and Suppl. Fig. 1F), SAT (Table 3 and Suppl. Fig. 1G), liver (Table 3 and Suppl. Fig. 1H), and peri-renal (Table 3 and Suppl. Fig. 1I) with no differences between the AUCs. Interestingly, WC cutoff values varied from 80.475 cm for TG content in SAT to 91.75 cm in the liver, whereas DXA-VAT and MRI-VAT showed lower values for peri-renal and SAT TG content (279.0g and 34.58g, for DXA and MRI respectively). On the other hand, the highest DXA-VAT cutoff value was detected for TG content in VAT (478g), while the highest cutoff value for MRI-VAT was observed in liver TG content (61.5g).

Cutoff values from ROC analyses suggested a WC range of 75.8–96.5 cm for increased CMR markers, the lowest values being for blood pressure (75.3 cm), the highest WC cutoff for insulin and HOMA-IR (96.5 cm), and the overall combined CMR cutoff value being 96.5 cm. Similar values were detected for HDL and TG (95.3 cm), whereas total and LDL cholesterol showed slightly lower cutoff values (82.65 and 80. 48, respectively). For DXA-VAT, the cutoff values ranged from 261g (LDL-c) to 753g for HDL and TG (261g for CMR analysis) and 1109g for IL-6. Most of the cutoff values were within the 261–269g range. A similar variability was observed on MRI-VAT cutoff values. Insulin, HOMA-IR, TG, and HDL where cutoff values varied from 17.45g (IL-6) and 18.63g (LDL-c) to77.36g (insulin, HOMA-IR, and HDL), and the overall CMR cutoff was 51.9g.

4. Discussion

The primary aim of this study was to investigate whether different central adiposity measurements (WC, DXA-VAT, and MRI-VAT) could detect increased CMR in a group of healthy young adults. We sought to explore whether WC measurements were comparable to more accurate

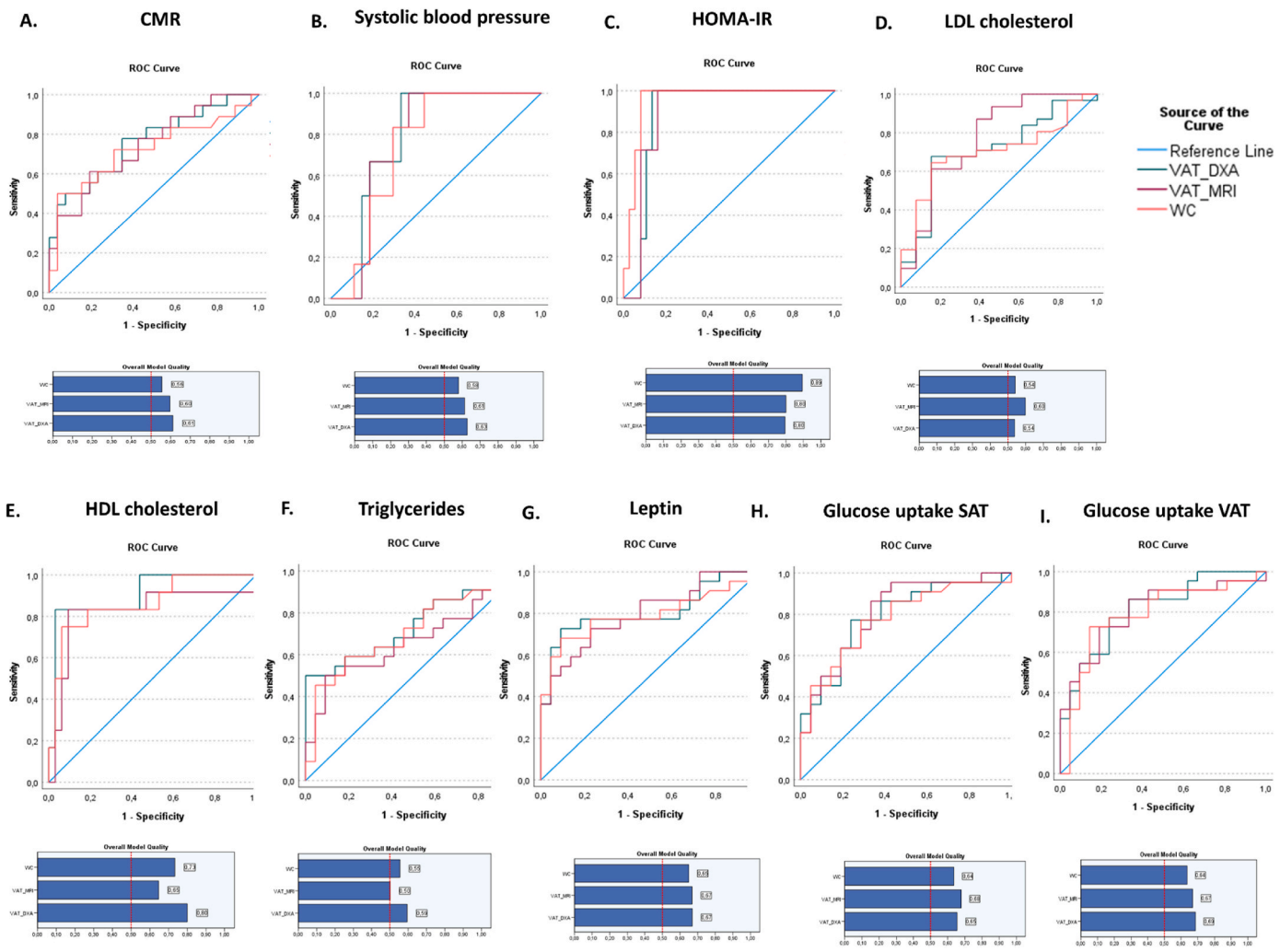

Fig. 2. Comparisons of WC, DXA-VAT, and MRI-VAT ROC curves for cardiometabolic risk markers.
Legend Fig. 2: ROC curves and overall model quality for CMR (A), Systolic blood pressure (B), HOMA-IR (C), LDL-cholesterol (D), HDL-cholesterol (E), triglycerides (F), leptin (G), glucose uptake (SUV) in subcutaneous adipose tissue (H), glucose uptake (SUV) in visceral adipose tissue (I).

VAT measurements (DXA-VAT and MRI-VAT) in terms of associations with classical CMR (lipid profile, HOMA-IR) markers and new markers, such as ^{18}F-FDG uptake in VAT and SAT, which have been shown to indicate the tissue's metabolic activity [41–43], along with TG content in different tissues. We observed that similar to DXA-VAT and MRI-VAT, WC displayed substantial positive correlations with various CMR markers, including LDL cholesterol, TG, insulin, and HOMA-IR, while exhibiting an inverse correlation with HDL cholesterol. All central adiposity measurements were also associated with cold-induced FDG uptake in SAT and VAT, considered early markers of CVD risk. In addition, ROC curve analysis indicates that all central adiposity measurements are equally good predictors for most CMR markers, showing similar AUCs for most variables and the combined CMR index variable. Remarkably, ROC analysis showed that these adiposity measurements could also predict increases in TG content in VAT, SAT, liver, and peri-renal, previously linked to a worsened cardiometabolic profile [31, 44].

Our findings of strong correlations between WC and CMR markers, in particular with the CMR combined index, align with earlier studies [45]. In a recent study, which included the offspring and third-generation cohorts of the Framingham health study, both WC and BMI could predict VAT-associated CMR in middle-aged men but not women [46]. Our study's ROC curve analysis suggested that WC could equally predict increases in CMR markers as the VAT estimated by DXA and MRI. Similarly, Katzmarzyk [47] observed higher AUCs for WC and VAT than other indexes, such as fat mass, percentage of body mass, and BMI, showing no statistical differences between DXA-VAT and WC when comparing the ability to predict increased CVD risk. Furthermore, even though no statistical differences were detected when comparing the AUCs, WC showed higher AUCs for both insulin and HOMA-IR than DXA-VAT and MRI-VAT. Similar to our data, where WC was presented as a good model for increased insulin and HOMA-IR in the ROC analysis, other researchers observed elevated correlations between glucose metabolism and WC [48,49]. Gautier et al. [45] and others reported that WC values could predict type 2 diabetes among men and women with baseline impaired fasting glucose. WC measurements were also shown to predict glucose deterioration in type 2 diabetes individuals [49]. On the other hand, other authors reported that DXA-VAT values showed a much more robust prediction of metabolic syndrome compared to WC among women with obesity [50]. These results somewhat differ from our study, in which all central adiposity measurements (WC, DXA- and MRI-VAT) were correlated with fasting glucose, insulin, and HOMA-IR. As normal fasting glucose was an inclusion criterion for our study, and there is no clear evidence of any deleterious cutoff point for glucose below 99 mg/dL, correlations between fasting glucose and central adiposity were not expected [1,2,11].

Regarding other clinical variables, all central adiposity measurements were associated with systolic blood pressure, as previously

Table 3
Comparison of waist circumference, DXA-VAT, and MRI-VAT ROC curves and cutoff values for clinical variables.

	AUC	SE	p-value	CI lower	CI higher	Cutoff value	Paired-sample comparison	p-value
• CMR[a]								
WC	0.723	0.086	**0.009**	0.555	0.891	96.475	WC x VAT-DXA	**0.368**
VAT-DXA	0.761	0.076	**<0.001**	0.612	0.910	261.00	WC x VAT-MRI	**0.507**
VAT-MRI	0.746	0.076	**<0.001**	0.597	0.597	51.945	VAT-DXA x VAT-MRI	**0.676**
• Systolic blood pressure								
WC	0.747	0.086	**0.004**	0.579	0.915	75.825	WC x VAT-DXA	**0.347**
VAT-DXA	0.784	0.079	**0.001**	0.628	0.940	261.000	WC x VAT-MRI	**0.462**
VAT-MRI	0.772	0.080	**0.001**	0.614	0.929	30.026	VAT-DXA x VAT-MRI	**0.792**
• Diastolic blood pressure								
WC	0.679	0.092	**0.052**	0.498	0.859	75.825	WC x VAT-DXA	**0.941**
VAT-DXA	0.671	0.122	**0.160**	0.433	0.910	269.000	WC x VAT-MRI	**0.272**
VAT-MRI	0.707	0.087	**0.020**	0.537	0.877	30.026	VAT-DXA x VAT-MRI	**0.713**
• Insulin								
WC	0.774	0.100	**<0.01**	0.578	0.970	96.475	WC x VAT-DXA	**0.020**
VAT-DXA	0.691	0.121	**0.112**	0.455	0.928	682.5	WC x VAT-MRI	**0.288**
VAT-MRI	0.736	0.107	**0.02**	0.525	0.946	77.357	VAT-DXA x VAT-MRI	**0.239**
• HOMA-IR								
WC	0.954	0.03	**<0.001**	0.894	1.013	96.475	WC x VAT-DXA	**0.055**
VAT-DXA	0.892	0.049	**<0.001**	0.795	0.989	682.5	WC x VAT-MRI	**0.030**
VAT-MRI	0.896	0.049	**<0.001**	0.801	0.991	77.357	VAT-DXA x VAT-MRI	**0.845**
• Total cholesterol								
WC	0.683	0.096	**0.056**	0.495	0.872	82.65	WC x VAT-DXA	**0.476**
VAT-DXA	0.712	0.081	**0.009**	0.553	0.871	279.5	WC x VAT-MRI	**0.651**
VAT-MRI	0.7	0.087	**0.022**	0.529	0.871	34.582	VAT-DXA x VAT-MRI	**0.754**
• LDL-c								
WC	0.703	0.083	**0.014**	0.542	0.865	80.475	WC x VAT-DXA	**0.896**
VAT-DXA	0.71	0.088	**0.017**	0.538	0.882	261	WC x VAT-MRI	**0.228**
VAT-MRI	0.772	0.089	**0.002**	0.598	0.945	18.632	VAT-DXA x VAT-MRI	**0.208**
• HDL-c								
WC	0.865	0.067	**<0.001**	0.734	0.995	95.325	WC x VAT-DXA	**0.188**
VAT-DXA	0.906	0.054	**<0.001**	0.8	1.013	753.5	WC x VAT-MRI	**0.306**
VAT-MRI	0.823	0.09	**<0.001**	0.647	0.999	77.357	VAT-DXA x VAT-MRI	**0.086**
• Triglycerides								
WC	0.712	0.08	**0.008**	0.555	0.869	95.325	WC x VAT-DXA	**0.465**
VAT-DXA	0.744	0.076	**0.001**	0.594	0.893	753.5	WC x VAT-MRI	**0.243**
VAT-MRI	0.667	0.085	**0.048**	0.501	0.833	77.357	VAT-DXA x VAT-MRI	**0.061**
• MCP-1								
WC	0.594	0.132	**0.476**	0.336	0.852	88.45	WC x VAT-DXA	**0.876**
VAT-DXA	0.581	0.097	**0.400**	0.392	0.771	451.5	WC x VAT-MRI	**0.571**
VAT-MRI	0.65	0.132	**0.258**	0.39	0.91	61.847	VAT-DXA x VAT-MRI	**0.347**
• IL-6								
WC	0.525	0.134	**0.851**	0.263	0.787	69.825	WC x VAT-DXA	**0.601**
VAT-DXA	0.494	0.110	**0.958**	0.279	0.709	1109.5	WC x VAT-MRI	**0.663**
VAT-MRI	0.552	0.126	**0.679**	0.305	0.799	17.45	VAT-DXA x VAT-MRI	**0.254**
• Leptin								
WC	0.792	0.073	**<0.001**	0.649	0.936	86.75	WC x VAT-DXA	**0.717**
VAT-DXA	0.808	0.07	**<0.001**	0.67	0.946	394.5	WC x VAT-MRI	**0.828**
VAT-MRI	0.8	0.067	**<0.001**	0.669	0.93	34.582	VAT-DXA x VAT-MRI	**0.86**
• Glucose uptake SAT								
WC	0.778	0.072	**<0.001**	0.636	0.92	79.6	WC x VAT-DXA	**0.701**
VAT-DXA	0.792	0.07	**<0.001**	0.655	0.929	269	WC x VAT-MRI	**0.251**
VAT-MRI	0.81	0.067	**<0.001**	0.678	0.941	27.398	VAT-DXA x VAT-MRI	**0.625**
• Glucose uptake VAT								
WC	0.784	0.075	**<0.001**	0.636	0.931	85.375	WC x VAT-DXA	**0.443**
VAT-DXA	0.814	0.065	**<0.001**	0.686	0.941	269	WC x VAT-MRI	**0.598**
VAT-MRI	0.805	0.069	**<0.001**	0.67	0.941	38.083	VAT-DXA x VAT-MRI	**0.853**
• Triglyceride content VAT								
WC	0.826	0.069	**<0.001**	0.692	0.961	87.63	WC x VAT-DXA	**0.302**
VAT-DXA	0.787	0.072	**<0.001**	0.646	0.928	478.0	WC x VAT-MRI	**0.654**
VAT-MRI	0.810	0.065	**<0.001**	0.682	0.938	38.08	VAT-DXA x VAT-MRI	**0.581**
• Triglyceride content SAT								
WC	0.760	0.076	**0.001**	0.611	0.910	80.475	WC x VAT-DXA	**0.074**
VAT-DXA	0.676	0.075	**<0.001**	0.619	0.914	279.5	WC x VAT-MRI	**0.12**
VAT-MRI	0.715	0.081	**0.008**	0.555	0.874	34.58	VAT-DXA x VAT-MRI	**0.129**
• Triglyceride content liver								
WC	0.769	0.077	**0.001**	0.617	0.921	91.75	WC x VAT-DXA	**0.41**
VAT-DXA	0.736	0.083	**0.004**	0.574	0.898	343.0	WC x VAT-MRI	**0.895**
VAT-MRI	0.774	0.078	**<0.001**	0.620	0.928	61.85	VAT-DXA x VAT-MRI	**0.424**
• Triglyceride content peri-renal								
WC	0.902	0.059	**<0.001**	0.786	1.019	86.125	WC x VAT-DXA	**0.466**
VAT-DXA	0.917	0.051	**<0.001**	0.817	1.016	279.5	WC x VAT-MRI	**0.131**
VAT-MRI	0.857	0.065	**<0.001**	0.730	0.984	34.58	VAT-DXA x VAT-MRI	**0.033**

Paired-sample area difference under the receiver operating characteristic curve (ROC) curve.
CI: confidence interval.
SE: standard error.

[a] CMR: combined cardiometabolic risk (≤2 or ≥3 CMR factors).

described [51]. Remarkably, when ROC curve analyses were conducted, we observed good overall model quality for all central adiposity measurements (high sensitivity and low 1- specificity) for systolic but not diastolic blood pressure. Notably, all adiposity measurements correlated with lipoprotein profile and showed high and comparable AUCs for LDL, HDL, and circulating TG in ROC analyses, essential for CVD risk prevention [52]. No differences between the three measurements were detected when comparing the AUCs (values within the predefined equivalence margin of 0.05). These findings were somewhat similar to one study in which WC and waist-to-hip ratio showed the most remarkable prediction for CMR [53]. Moreover, one study with more than 600 postmenopausal women observed that DXA-derived abdominal fat mass and WC were good predictors of alterations in blood lipids [45]. However, one review failed to show this association with WC [54]. In our study, HDL AUCs were also comparable between the three central adiposity measurements, and the overall quality of the models was elevated for all central adiposity measurements.

This study found inverse associations between VAT and SAT FDG uptake with central adiposity measurements. Even though many studies have shown the metabolic differences between VAT and SAT, only in the last decades have researchers shown that the FDG uptake was also different between the tissues and could represent their different metabolic activities [41–43]. Indeed, it has been hypothesized that the VAT uptakes more FDG than SAT due to its higher metabolic activity, which is directly related to VAT's more inflammatory profile. It has been previously shown that ^{18}F-FDG uptake is increased in highly inflamed tissues because of macrophage infiltration [41–43], which suggests that it would be possible to measure the inflammation degree of VAT using ^{18}F-FDG and that this could be used as a biomarker for cardiometabolic diseases [55,56]. One study comparing metabolically healthy obese (MHO) with metabolically altered obese (MAO) and healthy leans observed similar ^{18}F-FDG VAT uptake in MHO and MAO but lower than in healthy lean subjects [56]. The authors also observed negative associations between VAT FDG uptake and whole-body adiposity independent of age and sex. In our sample, the glucose uptake in both VAT and SAT were associated with central adiposity. The ROC curves showed that the central adiposity was a good model to predict higher SUV by these tissues. Although one may argue that cold exposure could affect the FDG uptake in VAT and SAT, greater FDG uptake in VAT compared to SAT was also detected after cold exposure [57], and no changes in WAT depots were detected after a cold acclimation protocol, suggesting none or little effect of cold in these depots. Moreover, we observed strong positive correlations between WC, DXA-VAT, and MRI-VAT with the content of triglycerides in SAT, VAT, and peri-renal fat, as well as with fat liver content. Similarly, ROC analysis suggested that all central adiposity variables provided a good model for TG content in VAT, SAT, liver, and peri-renal, without any differences between WC, DXA-VAT, and MRI-VAT AUCs. We have previously shown that the content of triglycerides in other tissues, such as brown adipose tissue (BAT), is directly associated with adiposity and cardiovascular risk markers [31,44]. Of note, the associations of central adiposity with a greater peri-renal fat suggest the potential of this measurement as a predictor of cardiometabolic complications, as previously reported [58].

Though DXA-VAT and MRI-VAT, along with CT-VAT, are considered more accurate methods for evaluating visceral fat [23–25], WC measurements presented a similar degree of correlation with most clinical markers as imaging-estimated central adiposity measurements, and no significant differences were detected when ROC curves were compared. Notably, it has recently been suggested that a minimal bias of DXA-VAT should be detected compared to MRI and CT [45,59,60]. Moreover, it has been reported that DXA-VAT and MRI-VAT can show equivalent results when measured over an anatomically matched abdominal region [60]. When comparing DXA-VAT and MRI-VAT with WC, one study found correlations between the first two measurements than with WC [60], which the authors suggest may result from WC measurements incorporating subcutaneous adipose tissue. However, our data does not agree with the latter study, as the correlations between WC with DXA-VAT and MRI-VAT were all equally elevated.

This study has limitations. The cross-sectional design does not allow for establishing a causal relationship between variables, and the sample size is relatively small. Moreover, the cutoff values differ across variables, which is not ideal. However, most of the classical CMR markers showed similar cutoff values, in particular for WC. The same cutoff of 96.5 cm was detected for the overall CMR, insulin, and HOMA-IR and very similar values were observed for HDL and TG (95.3). Moreover, it is important to highlight that some of the CMR markers we analyzed may be more sensitive to increases in abdominal fat than others, explaining their differences. Moreover, two different imaging techniques were compared, and early CMR markers, such as FDG uptake adipose tissue, which has been linked to CMR, were included in this analysis. Even though there is not enough evidence on the role of TG content in adipose tissue, the analysis of different tissues, such as VAT and peri-renal, could be important in future CMR prediction.

This study aimed to understand whether WC measurements, DXA-VAT, and MRI-VAT could predict increased CMR markers equally. Our analysis revealed associations between these measurements and CMR markers, suggesting that they can all be used to detect increased CMR in this group of participants. Indeed, our results showed that even in a relatively young study population, WC displayed a similar prediction for increased CMR markers than DXA-VAT and MRI-VAT, as shown by the ROC analysis. In addition, WC showed slightly but non-significant greater AUC for HOMA-IR, which could indicate a potential for WC to detect early changes in glucose metabolism, at least in this sample. Moreover, all central adiposity measurements were correlated to FDG uptake in subcutaneous and visceral fat, suggesting a possible role of these measurements in assessing increased new CMR. Our results reinforce the importance of WC measurements as a simple and easily accessible tool for assessing increased CMR markers in clinical practice. Given its practicality and efficacy, we recommend routinely using WC measurements in primary care and health centers to assess cardiometabolic risk.

Author's contributions

MM-P, GRR, and GAN performed data collection. MM-P, GRR, PD, MTS, SRGF, and LAV performed data analysis and interpretation. GRR, MM-P, and LAV drafted the manuscript. MM-P supervised the study. All authors edited and approved the final manuscript.

Funding information

This study was financially supported by grants from the São Paulo Research Foundation (FAPESP). Grant numbers: #2013/07607-8; #2016/10616–7; #2017/22586-8; #2019/02055-3.

Acknowledgments

The authors thank all the study volunteers, the Nuclear Medicine Division, the Laboratory of Emergency Medicine, The Laboratory of Cell Signaling (ORCR, Unicamp), and the Laboratory of Population Studies of the University of São Paulo. We also thank Marcela Reymond Simões for her contribution to the manuscript. This study was financially supported by grants from the São Paulo Research Foundation (FAPESP). Grant numbers: #2013/07607-8; #2016/10616–7; #2017/22586-8; #2019/02055-3.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2024.103801.

References

[1] Després JP, Lemieux I, Bergeron J, Pibarot P, Mathieu P, Larose E, Rodés-Cabau J, Bertrand OF, Poirier P. Abdominal obesity and the metabolic syndrome: contribution to global cardiometabolic risk. Arterioscler Thromb Vasc Biol 2008; 28:1039–49.
[2] Després JP, Lemieux I. Abdominal obesity and metabolic syndrome. Nature 2006; 444:881–7.
[3] Grundy SM. Metabolic syndrome pandemic. Arterioscler Thromb Vasc Biol 2008; 28:629–36.
[4] Lavie CJ, De Schutter A, Parto P, Jahangir E, Kokkinos P, Ortega FB, Arena R, Milani RV. Obesity and prevalence of cardiovascular diseases and prognosis-the obesity paradox updated. Prog Cardiovasc Dis 2016;58:537–47.
[5] Dadson P, Ferrannini E, Landini L, Hannukainen JC, Kalliokoski KK, Vaittinen M, Honka H, Karlsson HK, Tuulari JJ, Soinio M, Salminen P, Parkkola R, Pihlajamäki J, Iozzo P, Nuutila P. Fatty acid uptake and blood flow in adipose tissue compartments of morbidly obese subjects with or without type 2 diabetes: effects of bariatric surgery. Am J Physiol Endocrinol Metab 2017;313:E175–82.
[6] Fox CS, Hwang SJ, Massaro JM, Lieb K, Vasan RS, O'Donnell CJ, Hoffmann U. Relation of subcutaneous and visceral adipose tissue to coronary and abdominal aortic calcium (from the Framingham Heart Study). Am J Cardiol 2009;104:543–7.
[7] Ibrahim MM. Subcutaneous and visceral adipose tissue: structural and functional differences. Obes Rev 2010;11:11–8.
[8] Gregor MF, Hotamisligil GS. Inflammatory mechanisms in obesity. Annu Rev Immunol 2011;29:415–45.
[9] Dadson P, Landini L, Helmiö M, Hannukainen JC, Immonen H, Honka MJ, Bucci M, Savisto N, Soinio M, Salminen P, Parkkola R, Pihlajamäki J, Iozzo P, Ferrannini E, Nuutila P. Effect of bariatric surgery on adipose tissue glucose metabolism in different depots in patients with or without type 2 diabetes. Diabetes Care 2016;39: 292–9.
[10] Rothney MP, Catapano AL, Xia J, Wacker WK, Tidone C, Grigore L, Xia Y, Ergun DL. Abdominal visceral fat measurement using dual-energy X-ray: association with cardiometabolic risk factors. Obesity 2013;21:1798–802.
[11] Alberti KG, Zimmet P, Shaw J. Metabolic syndrome–a new world-wide definition. A consensus statement from the international diabetes federation. Diabet Med 2006;23:469–80.
[12] Pischon T, Boeing H, Hoffmann K, Bergmann M, Schulze MB, Overvad K, van der Schouw YT, Spencer E, Moons KG, Tjønneland A, Halkjaer J, Jensen MK, Stegger J, Clavel-Chapelon F, Boutron-Ruault MC, Chajes V, Linseisen J, Kaaks R, Trichopoulou A, Trichopoulos D, et al. General and abdominal adiposity and risk of death in Europe. N Engl J Med 2008;359:2105–20.
[13] Nevill AM, Winter EM, Ingham S, Watts A, Metsios GS, Stewart AD. Adjusting athletes' body mass index to better reflect adiposity in epidemiological research. J Sports Sci 2010;28:1009–16.
[14] Coutinho T, Goel K, Corrêa de Sá D, Kragelund C, Kanaya AM, Zeller M, Park JS, Kober L, Torp-Pedersen C, Cottin Y, Lorgis L, Lee SH, Kim YJ, Thomas R, Roger VL, Somers VK, Lopez-Jimenez F. Central obesity and survival in subjects with coronary artery disease: a systematic review of the literature and collaborative analysis with individual subject data. J Am Coll Cardiol 2011;57:1877–86.
[15] Ping Z, Pei X, Xia P, Chen Y, Guo R, Hu C, Imam MU, Chen Y, Sun P, Liu L. Anthropometric indices as surrogates for estimating abdominal visceral and subcutaneous adipose tissue: a meta-analysis with 16,129 participants. Diabetes Res Clin Pract 2018;143:310–9.
[16] Cook Z, Kirk S, Lawrenson S, Sandford S. Use of BMI in the assessment of undernutrition in older subjects: reflecting on practice. Proc Nutr Soc 2005;64: 313–7.
[17] Schousboe JT, Langsetmo L, Schwartz AV, Taylor BC, Vo TN, Kats AM, Barrett-Connor E, Orwoll ES, Marshall LM, Miljkovic I, Lane NE, Ensrud KE. Osteoporotic fractures in men (MrOS) study research group comparison of associations of DXA and CT visceral adipose tissue measures with insulin resistance, lipid levels, and inflammatory markers. J Clin Densitom 2017;20:256–64.
[18] Fang H, Berg E, Cheng X, Shen W. How to best assess abdominal obesity. Curr Opin Clin Nutr Metab Care 2018;21:360–5.
[19] Goldberg EK, Fung EB. Precision of the hologic DXA in the assessment of visceral adipose tissue. J Clin Densitom 2020;23:664–72.
[20] Dobbelsteyn CJ, Joffres MR, MacLean DR, Flowerdew G. A comparative evaluation of waist circumference, waist-to-hip ratio and body mass index as indicators of cardiovascular risk factors. The Canadian Heart Health Surveys. Int J Obes Relat Metab Disord 2001;25:652–61.
[21] Ross R, Neeland IJ, Yamashita S, Shai I, Seidell J, Magni P, Santos RD, Arsenault B, Cuevas A, Hu FB, Griffin BA, Zambon A, Barter P, Fruchart JC, Eckel RH, Matsuzawa Y, Després JP. Waist circumference as a vital sign in clinical practice: a consensus statement from the IAS and ICCR working group on visceral obesity. Nat Rev Endocrinol 2020;16:177–89.
[22] Grundy SM, Neeland IJ, Turer AT, Vega GL. Waist circumference as measure of abdominal fat compartments. J. Obes. 2013;454285.
[23] van der Kooy K, Seidell JC. Techniques for the measurement of visceral fat: a practical guide. Int J Obes Relat Metab Disord 1993;17:187–96.
[24] Cheung AS, de Rooy C, Hoermann R, Gianatti EJ, Hamilton EJ, Roff G, Zajac JD, Grossmann M. Correlation of visceral adipose tissue measured by Lunar Prodigy dual X-ray absorptiometry with MRI and CT in older men. Intern. J Obes 2016;40: 1325–8.
[25] Messina C, Albano D, Gitto S, Tofanelli L, Bazzocchi A, Ulivieri FM, Guglielmi G, Sconfienza LM. Body composition with dual energy X-ray absorptiometry: from basics to new tools. Quant. Imaging Med. Surg. 2020;10:1687–98.
[26] Pescatori LC, Savarino E, Mauri G, Silvestri E, Cariati M, Sardanelli F, Sconfienza LM. Quantification of visceral adipose tissue by computed tomography and magnetic resonance imaging: reproducibility and accuracy. Radiol Bras 2019; 52:1–6.
[27] Andersson C, Vasan RS. Epidemiology of cardiovascular disease in young individuals. Nat Rev Cardiol 2018;15(4):230–40.
[28] Lloyd-Jones DM, Leip EP, Larson MG, D'Agostino RB, Beiser A, Wilson PW, Wolf PA, Levy D. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. Circulation 2006;113(6):791–8.
[29] Würtz P, Wang Q, Kangas AJ, Richmond RC, Skarp J, Tiainen M, Tynkkynen T, Soininen P, Havulinna AS, Kaakinen M, Viikari JS, Savolainen MJ, Kähönen M, Lehtimäki T, Männistö S, Blankenberg S, Zeller T, Laitinen J, Pouta A, Mäntyselkä P, Ala-Korpela M. Metabolic signatures of adiposity in young adults: Mendelian randomization analysis and effects of weight change. PLoS Med 2014; 11(12):e1001765.
[30] Monfort-Pires M, U-Din M, Nogueira GA, de Almeida-Faria J, Sidarta-Oliveira D, Sant'Ana MR, De Lima-Júnior JC, Cintra DE, de Souza HP, Ferreira SRG, Sapienza MT, Virtanen KA, Velloso LA. Short dietary intervention with olive oil increases Brown adipose tissue activity in lean but not overweight subjects. J Clin Endocrinol Metab 2021;106:472–84.
[31] Monfort-Pires M, Regeni-Silva G, Dadson P, Nogueira GA, U-Din M, Ferreira SRG, Sapienza MT, Virtanen KA, Velloso LA. Brown fat triglyceride content is associated with cardiovascular risk markers in adults from a tropical region. Front Endocrinol 2022;13:919588.
[32] Farvid MS, Ng TW, Chan DC, Barrett PH, Watts GF. Association of adiponectin and resistin with adipose tissue compartments, insulin resistance and dyslipidaemia. Diabetes Obes. Metab. 2005;7:406–13.
[33] Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28: 412–9.
[34] Wang Q, Wang Z, Yao W, Wu X, Huang J, Huang L, Sun Y. Anthropometric indices predict the development of hypertension in normotensive and pre-hypertensive middle-aged women in tianjin, China: a prospective cohort study. Med Sci Mon Int Med J Exp Clin Res: international medical journal of experimental and clinical research 2018;24:1871–9.
[35] Tikhonoff V, Casiglia E, Virdis A, Grassi G, Angeli F, Arca M, Barbagallo CM, Bombelli M, Cappelli F, Cianci R, Cicero AFG, Cirillo M, Cirillo P, Dell'oro R, D'elia L, Desideri G, Ferri C, Galletti F, Gesualdo L, Giannattasio C, et al. Prognostic value and relative cutoffs of triglycerides predicting cardiovascular outcome in a large regional-based Italian database. J Am Heart Assoc 2024;13(3):e030319.
[36] Wang F, Han L, Hu D. Fasting insulin, insulin resistance and risk of hypertension in the general population: a meta-analysis. Clinica chimica acta; international journal of clinical chemistry 2017;464:57–63.
[37] Arshi B, Tohidi M, Derakhshan A, Asgari S, Azizi F, Hadaegh F. Sex-specific relations between fasting insulin, insulin resistance and incident hypertension: 8.9 years follow-up in a Middle-Eastern population. J Hum Hypertens 2015;29(4): 260–7.
[38] de Lemos JA, Morrow DA, Sabatine MS, Murphy SA, Gibson CM, Antman EM, McCabe CH, Cannon CP, Braunwald E. Association between plasma levels of monocyte chemoattractant protein-1 and long-term clinical outcomes in patients with acute coronary syndromes. Circulation 2003;107(5):690–5.
[39] Said EA, Al-Reesi I, Al-Shizawi N, Jaju S, Al-Balushi MS, Koh CY, Al-Jabri AA, Jeyaseelan L. Defining IL-6 levels in healthy individuals: a meta-analysis. J Med Virol 2021;93(6):3915–24.
[40] Lloyd-Jones DM, Wilson PW, Larson MG, Beiser A, Leip EP, D'Agostino RB, Levy D. Framingham risk score and prediction of lifetime risk for coronary heart disease. Am J Cardiol 2004;94(1):20–4.
[41] Christen T, Sheikine Y, Rocha VZ, Hurwitz S, Goldfine AB, Di Carli M, Libby P. Increased glucose uptake in visceral versus subcutaneous adipose tissue revealed by PET imaging. JACC. Cardiovascular imaging 2010;3(8):843–51.
[42] Tahara N, Yamagishi S, Kodama N, Tahara A, Honda A, Nitta Y, Igata S, Matsui T, Takeuchi M, Kaida H, Kurata S, Abe T, Fukumoto Y. Clinical and biochemical factors associated with area and metabolic activity in the visceral and subcutaneous adipose tissues by FDG-PET/CT. The Journal of clinical endocrinology and metabolism 2015;100(5):E739–47.
[43] Pak, K., Santavirta, S., Shin, S., Nam, H-Y., De Maeyer, S., Nummenmaa, L. Glucose metabolism and Radiodensity of Abdominal Adipose Tissue: A 5-year longitudinal study in a large PET cohort. MedRxiv preprint doi: https://doi.org/10.1101/2024.01.21.24301581;.
[44] U-Din M, Ahmed BA, Syed SA, Ong FJ, Oreskovich SM, Gunn E, Surette MG, Punthakee Z, Steinberg GR, Morrison KM. Characteristics of abdominal visceral adipose tissue, metabolic health and the gut microbiome in adults. The Journal of Clinical Endocrinology and Metabolism 2024;109(3):680–90.
[45] Gautier A, Roussel R, Ducluzeau PH, Lange C, Vol S, Balkau B, Bonnet F, DESIR Study Group. Increases in waist circumference and weight as predictors of type 2 diabetes in individuals with impaired fasting glucose: influence of baseline BMI: data from the DESIR study. Diabetes Care 2010;33:1850–2.

[46] Kammerlander AA, Lyass A, Mahoney TF, Massaro JM, Long MT, Vasan RS, Hoffmann U. Sex differences in the associations of visceral adipose tissue and cardiometabolic and cardiovascular disease risk: the Framingham heart study. J Am Heart Assoc 2021;10:e019968.
[47] Katzmarzyk PT, Heymsfield SB, Bouchard C. Clinical utility of visceral adipose tissue for the identification of cardiometabolic risk in white and African American adults. The American journal of clinical nutrition 2013;97(3):480–6.
[48] Farin HM, Abbasi F, Reaven GM. Body mass index and waist circumference correlate to the same degree with insulin-mediated glucose uptake. Metabolism 2005;54:1323–8.
[49] Blaha MJ, Gebretsadik T, Shintani A, Elasy TA. Waist circumference, not the metabolic syndrome, predicts glucose deterioration in type 2 diabetes. Obesity 2008;16:869–74.
[50] Bi X, Seabolt L, Shibao C, Buchowski M, Kang H, Keil CD, Tyree R, Silver HJ. DXA-measured visceral adipose tissue predicts impaired glucose tolerance and metabolic syndrome in obese Caucasian and African-American women. Eur J Clin Nutr 2015;69:329–36.
[51] Kuciene R, Dulskiene V. Associations between body mass index, waist circumference, waist-to-height ratio, and high blood pressure among adolescents: a cross-sectional study. Sci Rep 2019;9(1):9493.
[52] Zhang T, Chen J, Tang X, Luo Q, Xu D, Yu B. Interaction between adipocytes and high-density lipoprotein:new insights into the mechanism of obesity-induced dyslipidemia and atherosclerosis. Lipids Health Dis 2019;18:223.
[53] Schneider HJ, Glaesmer H, Klotsche J, Böhler S, Lehnert H, Zeiher AM, März W, Pittrow D, Stalla GK, Wittchen HU, DETECT Study Group. Accuracy of anthropometric indicators of obesity to predict cardiovascular risk. The Journal of clinical endocrinology and metabolism 2007;92(2):589–94. 2007.
[54] Huxley R, Mendis S, Zheleznyakov E, Reddy S, Chan J. Body mass index, waist circumference and waist:hip ratio as predictors of cardiovascular risk–a review of the literature. Eur J Clin Nutr 2010;64:16–22. 2010.
[55] Virtanen KA, Lönnroth P, Parkkola R, Peltoniemi P, Asola M, Viljanen T, Tolvanen T, Knuuti J, Rönnemaa T, Huupponen R, Nuutila P. Glucose uptake and perfusion in subcutaneous and visceral adipose tissue during insulin stimulation in nonobese and obese humans. The Journal of clinical endocrinology and metabolism 2002;87(8):3902–10.
[56] Oliveira AL, Azevedo DC, Bredella MA, Stanley TL, Torriani M. Visceral and subcutaneous adipose tissue FDG uptake by PET/CT in metabolically healthy obese subjects. Obesity 2015;23(2):286–9.
[57] Hanssen MJ, van der Lans AA, Brans B, Hoeks J, Jardon KM, Schaart G, Mottaghy FM, Schrauwen P, van Marken Lichtenbelt WD. Short-term cold acclimation recruits Brown adipose tissue in obese humans. Diabetes 2016;65(5):1179–89.
[58] Cho IJ, Wi J, Lee SE, Kim DH, Pyun WB. Perirenal fat and kidney function deterioration in patients with acute decompensated heart failure. International journal of heart failure 2023;5(1):36–47.
[59] Brendle C, Werner MK, Schmadl M, la Fougère C, Nikolaou K, Stefan N, Pfannenberg C. Correlation of Brown adipose tissue with other body fat compartments and patient characteristics: a retrospective analysis in a large patient cohort using PET/CT. Acad Radiol 2018;25:102–10.
[60] Neeland IJ, Grundy SM, Li X, Adams-Huet B, Vega GL. Comparison of visceral fat mass measurement by dual-X-ray absorptiometry and magnetic resonance imaging in a multiethnic cohort: the Dallas Heart Study. Nutr Diabetes 2016;6:e221.