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Prevalence of Metabolic Syndrome by different definitions, and its association with type 2 diabetes, pre-diabetes, and cardiovascular disease risk in Brazil

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ABSTRACT

Background and aims: Metabolic Syndrome (MS) is increasing in developing countries. Different definitions of MS lead to discrepancies in prevalence estimates and applicability. We assessed the prevalence of MS as defined by the International Diabetes Federation (IDF), modified National Cholesterol Education Program Adult Treatment Plan III (Modified NCEP) and Joint Interim Statement (JIS); compared the diagnostic performance and association of these definitions of MS with pre-diabetes, type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) risk.

Methods: A total of 714 randomly selected subjects from Northeastern Brazil were investigated in a cross-sectional study. Sociodemographic, anthropometric, and clinical data were recorded. Diagnostic test performance measures assessed the ability of the different MS definitions to identify those with pre-diabetes, T2DM and increased CVD risk.

Results: The adjusted prevalence of MS was 36.1% applying the JIS criteria, 35.1% the IDF and 29.5% Modified NCEP. Women were more affected by MS according to all definitions. MS was significantly associated with pre-diabetes, T2DM and CVD risk following the three definitions. However, the JIS and IDF definitions showed higher sensitivity than the Modified NCEP to identify pre-diabetes, T2DM and CVD risk. The odds ratios for those conditions were not significantly different when comparing the definitions.

Conclusions: MS is highly prevalent in Brazil, particularly among those with pre-diabetes, T2DM, and high CVD risk. The IDF and JIS criteria may be better suited in the Brazilian population to identify pre-diabetes, T2DM and CVD risk. This may also signify the importance of the assessment of MS in clinical practice.

1. Introduction

Metabolic syndrome (MS) is characterized by a clustering of interrelated risk factors including abdominal obesity, hyperglycemia, hypertension, and dyslipidemia [1]. The condition is associated with an increased risk of type 2 diabetes mellitus (T2DM), cardiovascular events and deaths [2].

The prevalence of MS has grown worldwide, and it is estimated that approximately 20–25% of the world's population has MS [3]. In developing countries, especially in South America, rapid socioeconomic and demographic transitions have fostered great increases in obesity rates, sedentary lifestyles, as well as profound changes in dietary patterns [4]. Studies conducted in Latin American countries as Chile, Colombia, Mexico, Peru and Venezuela showed a high

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prevalence of MS, ranging from 12.3% to 42.7% [5–9]. In Brazil, according to a systematic review from 2013, the weighted mean prevalence of MS was 29.6% (range: 14.9%–65.3%) [10].

Different definitions of MS have been proposed so far and, therefore, prevalence estimates may vary substantially across populations, depending not only on their characteristics, but specially on the diagnostic criteria applied. The most commonly used definitions have been produced by the National Cholesterol Education Program Adult Treatment Panel III (NCEP) in 2001 [11], which was updated in 2005 by the American Heart Association/National Heart, Lung, and Blood Institute (Modified NCEP) [12], and the International Diabetes Federation (IDF) [13]. Even though the definitions share common features, several parameters differ, which leads to discrepancies in applicability, uniformity, and positive predictive value [14]. More recently, a Joint Interim Statement (JIS) issued by several scientific societies has attempted to develop a unifying definition of MS [2].

Although the MS has been considered a major global health problem, many uncertainties and controversies remain. MS has been pointed out as an ill-characterized entity, with no clear rationale for thresholds [15]. Furthermore, its value as a risk assessment tool for future cardiovascular disease (CVD) has been claimed as weak [16], or no greater than the sum of its components [17]. Although the syndrome is effective in predicting diabetes, its predictive value beyond that of glucose intolerance has also been questioned [15]. In Brazil, few studies have described the prevalence of MS and its determinants. More importantly, there is scarce information about the applicability and agreement of different definitions of MS, as well as their predictive value in the estimation of T2DM, pre-diabetes, and CVD risk in the Brazilian population. Therefore, we aimed to determine the prevalence of MS as defined by the Modified NCEP [12], the IDF [13], and JIS [2]; assess the agreement between the definitions; and investigate the association of MS with pre-diabetes, T2DM and CVD risk. It was hypothesized that the JIS will show a higher prevalence of MS, as well as greater sensitivity to predict the cases of diabetes, pre-diabetes, and high CVD risk.

2. Subjects

This population-based study was conducted in the city of Pindoretama, in the northeast region of Brazil, between August 2012 and January 2013. The recruitment methods and examination procedures have been described beforehand [18]. The data were collected in the six main health centers located throughout the city. Subjects of both genders, aged ≥20 years, able to verbally communicate and willing to participate were eligible to enter the study. Exclusion criteria were those with acute or chronic severe cardiac, renal, or hepatic illness, pregnant women, and physically or mentally disabled individuals.

A registry list with the names of Pindoretama's citizens in alphabetic order was provided by the health authorities and used to select the potential participants. Random numbers were produced with the software R [19] and identified with the names in the list subsequently. Eight hundred and six subjects were randomly selected and of these, 714 agreed to participate (response rate of 88.6%). Owing to the different criteria applied by each MS definition, the total number of recorded observations was n = 707 following the IDF, and n = 704 according to both the Modified NCEP and JIS definitions. On recruitment, participants were requested by the community health workers to visit a nearby health center, after an overnight fast of 8–10 h. Sociodemographic, clinical, and nutritional data were collected by trained interviewers using pre-tested questionnaires. Anthropometric, blood pressure (BP) and body fat percentage (BF%) measurements were also taken.

3. Materials and methods

3.1. Measurements

Anthropometric measurements including height, weight, waist circumference (WC) and hip circumference (HC) were taken with subjects standing in bare feet and with light clothes. Weight was taken by using a portable digital scale, calibrated before use, placed on a flat surface, and recorded to the nearest 0.1 Kg. A well-mounted stadiometer was applied to measure height, with the participant looking straight and in erect position. Height was recorded to the nearest 0.1 cm. The body mass index (BMI) was estimated as the weight in kilograms divided by the square of height in meters (Kg/m^2). The BF% was assessed by a portable bipolar body fat analyzer (Omron®, Model HBF-306, Omron Healthcare, Inc., Illinois, United States). The WC was measured with a non-stretchable tape, positioned horizontally midway between the lower border of the ribs and iliac crest, on the mid-axillary line. The HC was assessed by placing the same tape at the greatest protrusion of the buttocks, with the subject standing straight. WC and HC were registered to the nearest 0.1 cm. The waist-to-hip ratio (WHR) was calculated as the WC divided by the HC. The BP was estimated twice, by using an electronic sphygmomanometer (Omron® BP785 IntelliSense® Automatic Blood Pressure Monitor with ComFitTM Cuff, Omron Healthcare, Inc., Illinois, United States). The first measurement was taken after a resting time of at least 15 min, and the second about 10 min after the first. The mean of the two values was used for analysis.

On arrival at the field center, a 10-mL fasting venous blood sample was collected for measuring fasting plasma glucose (FPG) levels and other relevant laboratory tests. Two hours after a 75 g oral glucose load, another venous sample was drawn for the oral glucose tolerance test (OGTT). Fasting and 2-h plasma glucose levels were assessed by the glucose oxidase method, whereas fasting insulin was determined by chemiluminescence. Total cholesterol (TC) was estimated by the cholesterol oxidase - phenol + aminophenazone (CHOD-PAP) method, while high-density lipoprotein cholesterol (HDL-C) was determined by a homogenous enzymatic colorimetric method. Triglycerides (TG) were determined by the glycerol-3-phosphate oxidase - phenol + aminophenazone (GPO-PAP) method. Low-density lipoprotein cholesterol (LDL-C) was calculated by the Friedewald Formula [20]. Laboratory quality control was assessed internally and externally.

3.2. Definition of variables and outcomes

MS was defined following the diagnostic criteria as suggested by the Modified NCEP [12], IDF [13], and JIS [2]. The three definitions are described in Table 1. Contrary to the Modified NCEP and JIS definitions, IDF considers abdominal obesity a prerequisite for diagnosing MS. Furthermore, the IDF definition applies ethnic-specific WC cut-off points as the measure of central obesity. For South and Central Americans, until population-specific data are available, IDF recommends using South Asian cut-off points, i.e., WC ≥ 90 cm in men and ≥80 cm in women. Therefore, for the Modified NCEP definition, the WC cut-off points applied in this study were ≥102 cm in men and ≥88 cm in women, whereas for the IDF definition were WC ≥ 90 cm in men and ≥80 cm in women. The JIS definition recommends that the IDF cut points for central obesity should be used for non-Europeans in case there is no country-specific data available. Since no WC cut-off points of risk for MS have been established for the Brazilian population, the IDF recommended cut points were also used here for the JIS definition.

Physical activity data were assessed by the International Physical Activity Questionnaire (IPAQ) short form [21]. Following the

Table 1
Criteria for clinical diagnosis of the MS following different definitions.

Risk Factors	IDF	Modified NCEP	JIS
Criteria for Diagnosis of MS	Abdominal obesity plus 2 or more risk factors	Any 3 or more of 5 risk factors	Any 3 or more of 5 risk factors
1 Central Obesity	WC ≥ 90 cm in males, ≥ 80 cm in females	WC ≥ 102 cm in males, ≥ 88 cm in females	WC ≥ 90 cm in males, ≥ 80 cm in females
2 TG	≥1.7 mmol/l (150 mg/dl) or on specific treatment for elevated TG	≥1.7 mmol/l (150 mg/dl) or on drug treatment for elevated TG	≥1.7 mmol/l (150 mg/dl) or on drug treatment for elevated TG
3 HDL-C	<1.03 mmol/l (40 mg/dl) in males, < 1.30 mmol/l (50 mg/dl) in females or on drug treatment for reduced HDL-C	<1.03 mmol/l (40 mg/dl) in males, < 1.30 mmol/l (50 mg/dl) in females or on drug treatment for reduced HDL-C	<1.03 mmol/l (40 mg/dl) in males, < 1.30 mmol/l (50 mg/dl) in females or on drug treatment for reduced HDL-C
4 Blood Pressure	SBP ≥ 130 mmHg or DBP ≥ 85 mmHg or treatment of previously diagnosed hypertension	SBP ≥ 130 mmHg or DBP ≥ 85 mmHg or current use of antihypertensive drugs in a patient with a history of hypertension	SBP ≥ 130 mmHg or DBP ≥ 85 mmHg or antihypertensive drug treatment in a patient with a history of hypertension
5 FG	Fasting plasma glucose ≥ 5.6 mmol/l (100 mg/dl) or previously diagnosed Type 2 diabetes	≥5.6 mmol/L (100 mg/dL) or on drug treatment for elevated glucose	≥5.6 mmol/L (100 mg/dL) or on drug treatment for elevated glucose

DBP: Diastolic Blood Pressure. FG: Fasting Glucose. HDL-C: High-Density Lipoprotein Cholesterol. IDF: International Diabetes Federation. JIS: Joint Interim Statement. MS: Metabolic Syndrome. NCEP: National Cholesterol Education Program Expert Panel. SBP: Systolic Blood Pressure. TG: Triglycerides. WC: Waist Circumference.

Brazilian Institute of Geography and Statistics (IBGE) classification, ethnicity was defined according to the participants' self-perception of their skin color. The different ethnic groups were categorized into "white", "brown", and "black" [22].

The 1999 WHO criteria were applied in diagnosing diabetes mellitus, impaired fasting glycaemia (IFG) and/or impaired glucose tolerance (IGT). Diabetes cases were those who were previously diagnosed, or those with fasting (venous) plasma glucose value ≥ 7.0 mmol/l (≥126 mg/dl), or the plasma glucose value 2 h after a 75 g oral glucose load ≥ 11.1 mmol/l (≥200 mg/dl), or both. IGT was determined when FPG <7.0 mmol/l (<126 mg/dl), and 2-h plasma glucose ≥7.8 mmol/l (≥140 mg/dl), but <11.1 mmol/l (<200 mg/dl). IFG was defined as FPG ≥6.1 mmol/l (≥110 mg/dl), but <7.0 mmol/l (<126 mg/dl), and 2-h plasma glucose <7.8 mmol/l (<140 mg/dl). Individuals with IFG and/or IGT were classified as pre-diabetes cases [23].

Dyslipidemia was described as TG ≥ 1.7 mmol/l and HDL-C < 0.9 mmol/l for men; and <1.0 mmol/l for women [23]. Insulin resistance was calculated with the homeostasis model assessment of insulin resistance (HOMA-IR = [insulin (mU/l) × glucose (mmol/l)]/22.5) [24]. The 10-year risk of CVD was calculated for each participant using a 2008 Framingham risk equation. The model predictors for the gender-specific algorithm included age, TC, HDL-C, systolic BP, antihypertensive medication use, smoking and diabetes status [25]. Individuals with a Framingham predicted risk for an incident cardiovascular event of 10% or above during the next 10 years were described as having high CVD risk. Thirteen subjects reported a history of stroke and/or myocardial infarction and were excluded from the analysis for CVD risk.

3.3. Ethics

The study was carried out according to the guidelines laid down in the Declaration of Helsinki [26], and the protocol was approved by both the local Ethical Committee in Brazil (Protocol Number: 045.06.12) and the Regional Committee for Medical and Health Research Ethics (REK) in Norway (Reference: 2012/779/REK sør-øst D). Written or verbal consent was obtained from each subject before any investigation. The participants were also informed of their right to withdraw from the study at any stage, or to omit their data from the analysis. All the names in the registration list were removed before the analyses were performed. Those diagnosed with any clinical condition were referred to the nearest health center for proper treatment and further follow up.

3.4. Statistical Analysis

Means and 95% confidence interval (CI) were given for numerical data, while percentages and 95% CI for categorical variables. Generalized linear regression models (GLM) were fitted to the data after adjusting for age and gender. In particular, we fitted GLMs with linear link function for comparing differences between adjusted means and GLMs with the logit link function to compare differences between proportions. Following estimation of the adjusted logistic regression models, the prevalence of MS was obtained as margins. Kappa statistics measured the agreement between the three MS definitions [27]. Diagnostic test performance measures including sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) were calculated using contingency tables. Adjusted odds ratios (ORs) were calculated based on the IDF, Modified NCEP and JIS definitions for pre-diabetes, T2DM, and CVD risk. Adjusted ORs were obtained by applying logistic regression analysis controlling for age, gender, and BMI. The significance level was set at 0.05. All tests were two-sided. Statistical analyses were performed by using SPSS 25th version [28] and Stata 15th edition [29].

4. Results

As can be seen in Table 2, substantial differences were found in demographic, lifestyle, anthropometric and cardiometabolic characteristics between those with and without MS. Comparing only those with MS, the mean WC (p-value: 0.035) and BMI (p-value: 0.039) were significantly higher using the Modified NCEP criteria than when the JIS definition was applied.

Irrespective of which definition was applied, the prevalence of MS among women (ranging from 38.2 to 44.8%) was significantly higher than in men (ranging from 12.6 to 18.9%) (Table 3). According to all three definitions, the prevalence increased significantly with age, BMI status, and level of income. However, the prevalence did not differ significantly among ethnic groups. Using the Modified NCEP definition, those with ≥10 years of education showed a significantly lower odds for MS than those with <10 years (OR = 0.6, 95% CI: 0.4–0.9; p-value: 0.019).

Table 4 shows the overall prevalence of MS, as well as the prevalence of MS among those with pre-diabetes, T2DM and high CVD risk. The age- and gender-adjusted prevalence was highest applying the definition described by the JIS (36.1%), followed by the IDF (35.1%) and Modified NCEP (29.5%). Nevertheless, these

Table 2
Cardiometabolic, anthropometric and lifestyle characteristics of the study participants with and without MS, applying the criteria as described by the IDF, Modified NCEP and JIS.

Variables	IDF[a]		Modified NCEP[a]		JIS[a]	
	With MS	**Without MS**	**With MS**	**Without MS**	**With MS**	**Without MS**
n	248	459	208	496	254	450
Age (years)	52.4 (50.5–54.3)**	41.1 (39.7–42.5)	53.0 (50.8–55.1)**	41.8 (40.5–43.2)	52.7 (50.8–54.6)**	40.9 (39.4–42.3)
Gender (female), % (95% CI)	84.1 (79.6–88.5)**	55.6 (51.0–60.1)	87.1 (82.7–91.5)**	56.7 (52.3–61.1)	84.2 (79.9–88.6)**	55.1 (50.5–59.8)
Smoking (yes)[b]	36.5 (30.9–42.1)	41.7 (37.4–46.0)	37.7 (31.6–43.9)	40.9 (36.8–45.0)	36.5 (30.9–42.0)	42.1 (37.7–46.4)
Alcohol Consumption (yes)	39.2 (32.9–45.4)	34.9 (30.9–38.9)	39.8 (32.9–46.6)	35.0 (31.2–38.8)	39.0 (32.8–45.1)	35.0 (31.0–39.0)
Physical Activity						
Low	77.2 (71.5–82.8)**	61.1 (56.6–65.7)	82.2 (76.6–87.9)**	60.2 (55.8–64.6)	77.3 (71.7–82.9)**	60.6 (56.0–65.2)
Moderate/High	22.8 (17.2–28.5)	38.9 (34.3–43.4)	17.8 (12.1–23.4)	39.8 (35.4–44.2)	22.7 (17.1–28.3)	39.4 (34.8–44.0)
BMI (kg/m^2)	29.6 (28.9–30.2)**	25.4 (25.0–25.9)	30.4 (29.7–31.0)**	25.4 (25.0–25.9)	29.4 (28.8–30.0)**	25.5 (25.0–25.9)
WC (cm)	97.2 (95.7–98.8)**	86.1 (85.0–87.2)	98.9 (97.3–100.6)**	86.4 (85.3–87.4)	96.7 (95.1–98.2)**	86.4 (85.2–87.5)
WHR, mean (95% CI)	0.95 (0.94–0.96)**	0.90 (0.89–0.91)	0.96 (0.95–0.97)**	0.90 (0.89–0.91)	0.95 (0.93–0.96)**	0.90 (0.89–0.91)
BF%, mean (95% CI)	35.1 (34.2–36.0)**	31.5 (30.9–32.2)	35.6 (34.6–36.6)**	31.7 (31.1–32.3)	34.9 (34.0–35.8)**	31.7 (31.0–32.3)
SBP (mmHg)	137.2 (134.9 –139.6)**	122.5 (120.8 –124.2)	138.4 (135.8 –141.0)**	123.2 (121.5 –124.8)	137.7 (135.4 –140.0)**	122.0 (120.3 –123.7)
DBP (mmHg)	83.9 (81.7–86.1)**	72.9 (71.3–74.4)	83.3 (80.8–85.7)**	74.0 (72.5–75.6)	84.0 (81.9–86.2)**	72.7 (71.1–74.3)
FPG (mmol/l)	6.5 (6.2–6.8)**	4.9 (4.7–5.1)	6.9 (6.5–7.2)**	4.9 (4.7–5.1)	6.6 (6.3–6.9)**	4.8 (4.6–5.1)
2-hour Post Glucose Load (mmol/l)	9.6 (9.1–10.2)**	6.9 (6.5–7.3)	10.3 (9.7–10.9)**	6.8 (6.5–7.2)	9.8 (9.2–10.3)**	6.8 (6.4–7.2)
Fasting Insulin (micro UI/ml)	8.6 (8.0–9.3)**	5.7 (5.2–6.2)	8.9 (8.2–9.6)**	5.8 (5.4–6.3)	8.5 (7.9–9.2)**	5.7 (5.3–6.2)
HOMA-IR	2.4 (2.3–2.6)**	1.2 (1.1–1.3)	2.6 (2.4–2.8)**	1.2 (1.1–1.4)	2.4 (2.2–2.6)**	1.2 (1.1–1.3)
Total Cholesterol (mmol/l)	5.0 (4.9–5.1)**	4.5 (4.4–4.6)	5.1 (4.9–5.2)**	4.6 (4.5–4.6)	5.0 (4.9–5.2)**	4.5 (4.4–4.6)
HDL-C (mmol/l)	1.19 (1.17–1.20)**	1.24 (1.23–1.26)	1.19 (1.17–1.20)**	1.24 (1.23–1.25)	1.18 (1.17–1.20)**	1.25 (1.23–1.26)
LDL-C (mmol/l)	2.9 (2.8–3.0)	2.8 (2.7–2.9)	3.0 (2.8–3.1)	2.8 (2.7–2.9)	2.9 (2.8–3.1)	2.8 (2.7–2.9)
Triglycerides (mmol/l)	2.4 (2.2–2.6)**	1.1 (0.9–1.2)	2.5 (2.3–2.7)**	1.1 (1.0–1.2)	2.4 (2.2–2.6)**	1.0 (0.9–1.1)
Dyslipidemia, % (95% CI)	56.8 (50.3–63.3)**	9.6 (7.0–12.2)	60.5 (53.5–67.5)**	11.3 (8.6–14.1)	58.6 (52.2–64.9)**	8.3 (5.9–10.7)

Data are mean (95% confidence interval) or percentage (95% confidence interval), adjusted for age and gender; [a] The number of observations recorded was 707 for the IDF definition, 704 for both Modified NCEP ATP III and JIS; [b] Included those who self-reported as being smokers or had stopped smoking for less than 1 year; The values were significantly different between those with and without MS at **p < 0.01 or *p < 0.05, by logistic regression analysis; BF%: Body Fat Percentage. BMI: Body Mass Index. CI: Confidence Interval. DBP: Diastolic Blood Pressure. FPG: Fasting Plasma Glucose. HDL-C: High-Density Lipoprotein Cholesterol. HOMA-IR: Homeostasis Model Assessment of Insulin Resistance. IDF: International Diabetes Federation. JIS: Joint Interim Statement. LDL-C: Low-Density Lipoprotein Cholesterol. MS: Metabolic Syndrome. NCEP: National Cholesterol Education Program Expert Panel. SBP: Systolic Blood Pressure. WC: Waist Circumference. WHR: Waist-to-Hip Ratio.

Table 3
Prevalence of MS by demographic and socioeconomic characteristics, age- and gender-adjusted.

	n	IDF	Modified NCEP	JIS
Gender				
Male	242	18.3 (13.6–23.0)**	12.6 (8.5–16.7)**	18.9 (14.2–23.7)**
Female	472	43.7 (39.5–47.9)	38.2 (34.1–42.3)	44.8 (40.7–49.0)
Age Groups				
20–35	235	18.5 (13.6–23.3)**	13.8 (9.4–18.1)**	18.5 (13.6–23.4)**
36–50	241	32.6 (26.9–38.4)	28.7 (23.2–34.2)	33.3 (27.6–39.1)
≥51	238	54.0 (48.1–60.0)	46.0 (40.0–51.9)	56.2 (50.2–62.1)
BMI Status				
<25 kg/m^2	272	16.7 (12.5–20.8)**	9.7 (6.4–13.1)**	18.7 (14.4–23.0)**
25–29.99 kg/m^2	266	38.5 (33.2–43.9)	30.9 (25.9–35.9)	38.9 (33.7–44.2)
≥30 kg/m^2	175	58.3 (51.6–64.9)	57.7 (51.2–64.3)	58.3 (51.7–64.9)
Ethnicity				
White	120	37.8 (29.9–45.8)	32.8 (25.1–40.5)	39.5 (31.6–47.4)
Brown	576	34.7 (31.2–38.3)	29.1 (25.7–32.5)	35.6 (32.1–39.2)
Black	18	27.8 (9.0–46.6)	22.2 (4.7–39.8)	27.8 (9.1–46.5)
Education				
<10 years	508	40.4 (36.5–44.4)	34.8 (31.0–38.6)*	41.8 (37.9–45.7)
≥10 years	206	22.0 (16.5–27.4)	16.7 (11.7–21.6)	22.1 (16.6–27.5)
Monthly Income				
<2 MW	641	34.2 (30.8–37.5)**	28.8 (25.6–31.9)**	35.2 (31.9–38.6)**
≥2 MW	71	44.3 (33.9–54.6)	37.7 (27.6–47.7)	44.9 (34.5–55.3)

Data are provided as % (95% confidence interval) adjusted for age and gender; **p < 0.001 and *p < 0.05, by logistic regression analysis; BMI: Body Mass Index. IDF: International Diabetes Federation. JIS: Joint Interim Statement. MS: Metabolic Syndrome. MW: Minimum Wage in 2012, that corresponds currently to US$ 162.00. NCEP: National Cholesterol Education Program Expert Panel.

estimates were not significantly different. Using the definition recommended by the JIS, MS was present in 58.2% of subjects diagnosed with pre-diabetes, 76.1% of those with T2DM, and 57.1% of those with high CVD risk. Following the IDF definition, the respective parameters were 57.1, 74.3, 54.8%, while for the Modified NCEP, the values were 46.9, 70.8, and 48.0%. The agreement was highest between the definitions described by the IDF and JIS, as measured by the kappa statistics (overall study population and pre-diabetes: 0.98; T2DM and high CVD risk: 0.95). The lowest agreement was observed between the IDF and Modified NCEP definitions, both for overall (0.83) and all other subsets of the study population (pre-diabetes: 0.76; T2DM: 0.82; high CVD risk: 0.77).

Table 4
Adjusted prevalence of MS among overall, subjects with pre-diabetes, T2DM and high CVD risk, as well as the agreement between the definitions of MS as described by the IDF, Modified NCEP and JIS.

	IDF		Modified NCEP	JIS	IDF vs. Modified NCEP	Modified NCEP vs. JIS	IDF vs. JIS
	n	% (95% CI)	% (95% CI)	% (95% CI)	Kappa (p-value)	Kappa (p-value)	Kappa (p-value)
Overall	714	35.1 (31.9–38.3)	29.5 (26.5–32.6)	36.1 (32.9–39.3)	0.83 (<0.001)	0.85 (<0.001)	0.98 (<0.001)
Pre-Diabetes	100	57.1 (48.0–66.3)	46.9 (37.8–56.1)	58.2 (49.1–67.2)	0.76 (<0.001)	0.78 (<0.001)	0.98 (<0.001)
T2DM	114	74.3 (66.9–81.8)	70.8 (63.2–78.4)	76.1 (68.9–83.3)	0.82 (<0.001)	0.86 (<0.001)	0.95 (<0.001)
High CVD Risk[a]	254	54.8 (49.3–60.2)	48.0 (42.6–53.4)	57.1 (51.8–62.5)	0.77 (<0.001)	0.82 (<0.001)	0.95 (<0.001)

Data presented as percentage (95% confidence interval) adjusted for age and gender.
[a] The 10-year risk of CVD was calculated using a 2008 Framingham risk equation. Those with a history of stroke and/or myocardial infarction were excluded from the analysis; CI: Confidence Interval. CVD: Cardiovascular Disease. IDF: International Diabetes Federation. JIS: Joint Interim Statement. MS: Metabolic Syndrome. NCEP: National Cholesterol Education Program Expert Panel. T2DM: Type 2 Diabetes Mellitus.

The diagnostic performances of the different MS definitions to diagnose pre-diabetes, T2DM and high CVD risk are presented in Table 5. The JIS definition showed a greater sensitivity than the Modified NCEP to identify pre-diabetes (58.2% vs 46.9%), T2DM (76.1% vs 70.8%) and high CVD risk (57.1% vs 48%). However, following the Modified NCEP definition, the specificity (pre-diabetes: 83.4%; T2DM: 78.3%; high CVD risk: 81.2%) and PPV (pre-diabetes: 31.5%; T2DM: 38.4%; high CVD risk: 59.1%) were higher than when the JIS definition was applied. The IDF and JIS definitions showed similar results regarding sensitivity, specificity, PPV and NPV.

Table 6 presents the ORs of the IDF, Modified NCEP and JIS definitions for pre-diabetes, T2DM, and high CVD risk using logistic regression analysis after adjustment for age, gender, and BMI. A significant association was found between MS and pre-diabetes, T2DM and high CVD risk, irrespective of which definition of MS was applied. The adjusted ORs for pre-diabetes (ranging from 3.6 to 3.9), T2DM (5.0–6.4) and high CVD risk (5.6–7.1) were not significantly different between the different definitions of MS.

Table 6
Odds rations (OR) for pre-diabetes, T2DM, and people with high CVD risk in those with MS compared with those without MS.

	Pre-Diabetes	T2DM	High CVD Risk
	OR (95% CI)	OR (95% CI)	OR (95% CI)
IDF	3.9 (2.3–6.5)[a]	5.0 (3.0–8.5)[a]	5.6 (2.9–10.9)[a]
Modified NCEP	3.6 (2.0–6.2)[a]	6.4 (3.7–11.1)[a]	5.7 (2.9–11.3)[a]
JIS	3.9 (2.3–6.5)[a]	5.4 (3.2–9.3)[a]	7.1 (3.6–14.2)[a]

Adjusted for age, gender, and body mass index.
[a] $p < 0.001$; CI: Confidence Interval. CVD: Cardiovascular Disease. IDF: International Diabetes Federation. JIS: Joint Interim Statement. MS: Metabolic Syndrome. NCEP: National Cholesterol Education Program Expert Panel. T2DM: Type 2 Diabetes Mellitus.

5. Discussion

To the best of our knowledge, this is one of the first population-based study from Brazil to compare the prevalence of MS among subjects with pre-diabetes, T2DM and high CVD risk, following the recent JIS criteria in relation to other more established definitions. We found a high prevalence of MS in the overall population, and particularly among the participants with pre-diabetes, T2DM, and high CVD risk. Women and those with a higher income were disproportionately affected. The agreement between all three definitions was almost perfect. The JIS and IDF definitions showed a higher sensitivity to identify the subjects with pre-diabetes, T2DM and high CVD risk.

In the current study, the observed prevalence of MS was higher than the estimated prevalence of 20–25% for the global population [3]. Following the Modified NCEP definition, the overall prevalence of MS in our study population (29.5%) was somewhat lower than that in the US population (34.7%), reported by the 2003–2012 National Health and Nutrition Examination Survey (NHANES) [30]. Compared to other middle-income countries, using the IDF

Table 5
Diagnostic performance of the IDF, Modified NCEP and JIS definitions of MS to predict pre-diabetes, T2DM, and people with high CVD risk in an adult Brazilian population.

	Pre-Diabetes	T2DM	High CVD Risk
IDF			
Sensitivity, % (95% CI)	57.1 (46.8–67.1)	74.3 (65.3–82.1)	54.8 (48.4–61.0)
Specificity, % (95% CI)	78.2 (74.3–81.8)	72.4 (68.6–76.0)	76.6 (72.3–80.5)
Positive Predictive Value, % (95% CI)	29.9 (22.9–37.7)	33.9 (28.0–40.2)	57.1 (50.5–63.4)
Negative Predictive Value, % (95% CI)	91.8 (88.8–94.2)	93.7 (91.0–95.7)	74.9 (70.6–78.9)
Accuracy (%)	75.2	72.7	68.7
Modified NCEP			
Sensitivity, % (95% CI)	46.9 (36.8–57.3)	70.8 (61.5–79.0)	48.0 (41.7–54.4)
Specificity, % (95% CI)	83.4 (79.8–86.6)	78.3 (74.8–81.6)	81.2 (77.2–84.7)
Positive Predictive Value, % (95% CI)	31.5 (23.4–40.5)	38.4 (31.7–45.4)	59.1 (52.0–66.0)
Negative Predictive Value, % (95% CI)	90.6 (87.6–93.1)	93.4 (90.8–95.4)	73.3 (69.2–77.2)
Accuracy (%)	78.3	77.1	69.2
JIS			
Sensitivity, % (95% CI)	58.2 (47.8–68.1)	76.1 (67.2–83.6)	57.1 (50.8–63.3)
Specificity, % (95% CI)	77.5 (73.5–81.1)	71.6 (67.8–75.2)	76.6 (72.3–80.5)
Positive Predictive Value, % (95% CI)	29.6 (22.7–37.3)	33.8 (28.0–40.0)	58.0 (51.6–64.3)
Negative Predictive Value, % (95% CI)	91.9 (88.9–94.3)	94.0 (91.4–96.0)	75.9 (71.6–79.8)
Accuracy (%)	74.8	72.3	69.5

CI: Confidence Interval. CVD: Cardiovascular Disease. IDF: International Diabetes Federation. JIS: Joint Interim Statement. MS: Metabolic Syndrome. NCEP: National Cholesterol Education Program Expert Panel. T2DM: Type 2 Diabetes Mellitus.

definition, our estimate of 35.1% (18.3% in men; 43.7% in women) was similar to that reported from Colombia 32.9% [6], lower than Mexico (49.8%) [31], higher than India (25.8%) [32] and China (9.8% in men; 16.6% in women) [33]. According to the JIS definition, 36.1% of the subjects were classified as having MS, which was slightly higher than that observed in central Brazil (32%) [34]. In addition to methodological differences, the varied prevalence rates of MS across populations may be explained by different demographic, epidemiological and nutritional transitions [35], as well as environmental, social [36] and ethnic disparities [37].

Although the prevalence of MS did not differ significantly between the three definitions, it was highest when using the criteria described by the JIS and lowest following the Modified NCEP. The observed higher prevalence of MS obtained using the JIS criteria compared to the Modified NCEP may be due to the higher rate of central obesity identified by the lower WC cut points used for the JIS [2]. Furthermore, the MS prevalence was also somewhat higher according to the IDF definition than the Modified NCEP definition. The IDF criteria places more emphasis on central obesity in the definition of the MS and recommends lower WC cut-off points for South America similarly to the JIS definition [13].

Following all three definitions, the prevalence of MS was significantly higher among women than men, which has also been found elsewhere [31,33,38]. This was especially evident for the prevalence following the IDF (43.7% vs 18.3%; p-value < 0.001) and JIS (44.8% vs 18.9%; p-value < 0.001) definitions. Central obesity has been strongly correlated with insulin resistance and MS [13]. In our study population, as shown in Supplementary Table 1, women had a significantly higher prevalence of abdominal obesity when applying both the different recommended WC cut-off points of $\geq$90 cm for males; $\geq$ 80 cm for females (81.7% vs 52.1%) and of $\geq$102 cm for males; $\geq$ 88 cm for females (56.9% vs 14.9%). Furthermore, women also showed significantly higher rates of abnormalities in glucose metabolism (27.8% vs 18.7%) and HDL-C levels (73.5% vs 4.1%) (Supplementary Table 1). Nevertheless, this gender difference was not observed in another study conducted among 2130 adults in central Brazil [34]. The study involved a younger population, with less than 12,5% of women aged $\geq$50 years, compared to approximately 33% in our data. Furthermore, metabolic changes related to menopause have been linked to an increased risk of MS and CVD [39] and might also explain the higher prevalence of MS among females in our findings.

In this study, the prevalence of MS increased significantly and progressively with age and BMI status, which has been found by several [31,34,40,41]. In contrast with some studies from Southeastern Brazil [42,43], we identified an increasing rate of MS with higher levels of income, following all the definitions. Nevertheless, a study from India among 1178 adults, aged 20–80 years, also found that middle-to-high income significantly contributed to increased risk of MS [44]. In our sample, ethnicity was not an important predictor of MS. One possible reason may be the high degree of heterogeneity and mixed genetic composition of the Brazilian population. Due to five centuries of miscegenation, the country's population consists of interethnic admixtures of people from European, African and native American origins [45]. Although the relative genetic contribution of these diverse ethnic backgrounds may vary across the different regions in Brazil, a study from the Southeast among 1507 individuals found similar results [42].

Consistent with other studies [38,46,47] and as expected, we observed a higher frequency of MS among the subjects diagnosed with pre-diabetes, T2DM and high CVD risk. In our data, the highest prevalence of MS was observed when the JIS definition of MS was applied, possibly because abdominal obesity is not mandatory in this definition. Pre-diabetes and T2DM are known risk factors for atherosclerotic CVD [48], and the MS in T2DM patients is significantly associated with macro- and microvascular complications [46]. Recently Brazil has experienced a growing epidemic of obesity, hypertension, physical inactivity and T2DM. CVDs have become a major public health problem, since they constitute the main cause of death in the country [49]. Diabetes is a costly condition, and a large proportion of these expenditures are related to treating its complications. Intensive interventions involving multiple cardiovascular risk factors should be implemented to prevent or reduce the impact of further complications, which could potentially lead to health cost savings [50].

We examined the diagnostic performances of the different definitions of MS to identify those with pre-diabetes, T2DM, and people with high CVD risk. The JIS and IDF definitions presented higher sensitivity in the identification of participants with these 3 conditions. This difference may be due to the lower WC cut-off point applied by these definitions. These findings may indicate that applying the South Asian WC cut-offs as suggested by the IDF ($\geq$90 cm for males and $\geq$80 cm for females) in the definition of MS may be a better predictor for pre-diabetes, T2DM and CVD risk in our population.

This was a population-based study from a semi-urban area in Northeastern Brazil. The subjects were randomly selected, and the participation rate was high. Although the final sample was relatively small, it was large enough to meet the required sample size for analysis. The survey was performed by thoroughly trained and highly motivated personnel. Collection, transportation, and storage of the blood samples followed standard procedures and the analyses were performed in a certified laboratory. Considering the substantial socioeconomic, ethnic, and regional disparities in Brazil, generalization of our findings should be done with caution. However, since Brazilians have a mixed background in general, our sample might be a good representation of the country's population. Another limitation was the cross-sectional design of the study, as a cause-effect relationship could not be established. Therefore, long-term prospective studies are needed to confirm the association between the aforementioned factors and MS.

In conclusion, our study showed that MS is common in Brazil following the IDF, Modified NCEP and JIS definitions. Although all three definitions may be appropriate to assess the prevalence of MS, the IDF and JIS criteria may be better suited in the Brazilian population to predict pre-diabetes, T2DM and CVD risk. MS is highly prevalent among subjects with pre-diabetes, T2DM and CVD risk. Therefore, screening of MS in primary care centers, especially among women, may identify patients at higher risk of these conditions, and timely intensive multifactorial interventions could benefit this population.

Declaration of competing interest

The authors declare that they have no competing interests. This study received financial sponsorship from the University of Oslo and Ivar Helles Foundation. Nevertheless, the funders had no role in the study design; in the collection, analyses, or interpretation of data; in writing the report, or in the decision to publish the results.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2020.05.043.

Authors' contributions

Nayla Cristina do Vale Moreira contributed with the study concept and design, drafting of the article, as well as acquisition, analysis and interpretation of the data.

Akhtar Hussain contributed with the study concept and design, data analyses, writing the initial draft and revising it critically, study oversight and leadership.

Bishwajit Bhowmik participated in the analysis and interpretation of data, writing the article and revising it critically.

Ibrahimu Mdala contributed with the design of the study, writing the initial draft and revising it critically, as well as organized the database and conducted the statistical analysis.

Tasnima Siddiquee contributed with the design of the study, data curation and analyses, drafting of the article.

Virgínia Oliveira Fernandes contributed with conceptualizing the work and designing the methodology, data collection and analyses, writing the initial draft and revising it critically.

Renan Magalhães Montenegro Júnior contributed with the study concept and design, data analyses, study management and coordination, as well as writing the initial draft and revising it critically.

Haakon E. Meyer contributed with the design of the methodology, data analyses, study oversight and leadership, writing the initial draft and performing critical review.

All authors have read and approved the contents of the final manuscript. Furthermore, they have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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