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Metabolic syndrome: do clinical criteria identify similar individuals among overweight premenopausal women?

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Abstract

The purpose of this analysis was to determine to what extent the clinical criteria for metabolic syndrome (MetSyn) proposed by the World Health Organization (WHO), the European Group for Study of Insulin Resistance (EGIR), the National Cholesterol Education Program Adult Treatment Panel III (ATP III), and the International Diabetes Foundation (IDF); triglyceride (TG)/high-density lipoprotein cholesterol (HDL-C) ratio ≥3.0; and enlarged waist circumference (≥88 cm) and elevated TG (≥129 mg/dL) (EWET) identified similar or different overweight women and, secondarily, to examine the effect of 7% weight reduction on MetSyn status. Metabolic syndrome was determined among 256 premenopausal women (age = 41 ± 6 years, body mass index [BMI] = 32 ± 4 kg/m^2) participating in a dietary weight loss clinical trial based on the clinical criteria proposed by WHO, EGIR, ATP III, and IDF. The prevalence of TG/HDL-C ratio ≥3.0 and EWET was determined and compared with MetSyn status. Based on the clinical criteria, 16.1% (EGIR), 20.7% (WHO), 31.0% (ATP III), and 31.8% (IDF) of participants met the criteria for MetSyn; 30.3% and 31.8% had TG/HDL-C ≥3.0 and EWET, respectively. Between 77% and 99% of participants were similarly classified across the clinical criteria. The highest and lowest agreements were between ATP III and IDF (κ = 0.98; 95% confidence interval, 0.96-1.0) and WHO and IDF (κ = 0.39; 95% confidence interval, 0.26-0.51), respectively. The TG/HDL-C ratio ≥3.0 and EWET moderately agreed with all 4 clinical criteria for MetSyn (κ range, 0.36-0.59). Among those diagnosed with MetSyn at baseline, 64.0% to 75.0% of the participants who lost ≥7% and 25.8% to 55.6% of participants who lost <7% of their baseline body weight in 6 months no longer met the various clinical criteria for MetSyn, TG/HDL-C ≥3.0, or EWET. Our findings indicate that MetSyn varies substantially between clinical criteria, which raise questions about the clinical utility of these criteria. Regardless of MetSyn clinical criteria, ≥7% reduction in body weight has a beneficial impact on variables used to define MetSyn.

1. Introduction

Approximately 65% of US adults are overweight and 30% are obese [1]. Since 1994, the prevalence of overweight and obesity has increased by 9.2% and 7.5%, respectively [1]. Obesity is a known risk factor for cardiovascular disease (CVD), hypertension, and type 2 diabetes mellitus (DM) [2]. Obesity (either total body weight or intra-abdominal fat) is also closely linked to insulin resistance and the cluster of metabolic abnormalities referred to as the metabolic syndrome (MetSyn), both of which are also risk factors for CVD and type 2 DM [2,3]. However, not all overweight/obese individuals are insulin resistant or meet MetSyn criteria. It has been proposed that MetSyn classification is useful for identifying high-risk individuals who would benefit from more aggressive therapies. However, some have criticized its clinical utility because of the lack of consensual criteria [4-6].

Between 1998 and 2005, 4 organizations provided clinical criteria for diagnosing MetSyn (Table 1). The 1998 World Health Organization (WHO) clinical criteria required the presence of insulin resistance [7]. In 1999, the European Group for Study of Insulin Resistance (EGIR) proposed a simplified criteria for insulin resistance (>75th percentile of fasting plasma insulin of the population being studied) [8]. In 2001, the National Cholesterol Education Program Adult

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Table 1
Proposed clinical criteria for identifying women with increased CVD risk

Clinical measure	WHO	EGIR	ATP III	IDF	TG/HDL-C	EWET
Insulin resistance	IGT, FPG, type 2 DM, insulin resistance Plus any 2 or more of the following:	Plasma insulin >75th percentile Plus any 2 or more of the following:	None But any 3 of the following 5[a]:	None	None	None
Obesity						
WHR	>0.85 and/or					
WC (cm)		≥80	>88	Ethnicity specific[b]		≥88
BMI (kg/m^2)	BMI >30			Plus any 2 or more of the following:	BMI ≥25	
Blood lipids					None	
TG (mg/dL)	≥150 and/or	>180 or	≥150	≥150 or		≥129
HDL-C (mg/dL)	<39	<40 or lipid medication	<50 or lipid medication[c]	<50 or lipid medication		
Blood pressure					None	None
Systolic (mm Hg)	≥140	≥140	≥130	≥130 or		
Diastolic (mm Hg)	≥90	≥90 or BP medication	≥85 or BP medication[c]	≥85 or BP medication		
Glucose					None	None
IGT (mg/dL)	<126, or					
FPG (mg/dL)	110-126, or	≥110 but not type 2 DM	≥100[b] or type 2 DM[c]	≥100 or type 2 DM		
Type 2 DM	type 2 DM					
Other	Microalbuminuria				TG/HDL-C ratio ≥3.0	None

IGT indicates impaired glucose tolerance; FPG, fasting plasma glucose; WHR, waist to hip ratio; WC, waist circumference; BP, blood pressure.

[a] The 5 components of ATP III proposed clinical criteria of MetSyn are obesity, TG, HDL-C, blood pressure, and plasma glucose.

[b] Ethnicity-specific waist circumferences: Europid, ≥80 cm; South Asian and Chinese, ≥80 cm; Japanese, ≥90 cm.

[c] Modified from the original ATP III proposed clinical criteria of MetSyn. In the 2001 clinical criteria, impaired fasting glucose was set at >110 mg/dL; and blood lipids and pressure medication were not included in the original clinical criteria.

Treatment Panel III (ATP III) introduced a clinical criteria that eliminated the insulin resistance requirement but required the presence of 3 out of 5 equally weighed metabolic abnormalities (revised in 2004 to include an updated definition of impaired fasting glucose) [4,9,10]. In 2005, the International Diabetes Foundation (IDF) modified the ATP III clinical criteria and emphasized ethnic-specific cutoffs for waist circumference [11]. The IDF required the presence of enlarged waist circumference (EW) for the clinical diagnosis of MetSyn.

An underlying concept of these clinical criteria for MetSyn is to help identify individuals who are insulin resistant and at increased risk for CVD. However, some of the proposed clinical criteria require either a direct measurement of insulin resistance or the use of fasting insulin concentrations as a surrogate estimate of insulin resistance, neither of which are clinically practical. Obesity is a component of all clinical criteria for MetSyn; and as an alternative, it has been suggested [12] that the plasma triglyceride (TG)/high-density lipoprotein cholesterol (HDL-C) concentration ratio ≥3.0 can provide a clinically useful approach to identify overweight/obese individuals who are both insulin resistant and have the associated dyslipidemia that increases CVD risk [13]. Others have suggested the utilization of EW (≥88 cm) and elevated TG (ET, ≥129 mg/dL [1.45 mmol/L]) to help identify individuals who are insulin resistant [14-16]. Overweight status has been significantly correlated with steady-state plasma glucose, which provides a direct measure of insulin-mediated disposal of infused glucose [17]. High steady-state plasma glucose is analogous to a high degree of insulin resistance. Overweight status has also been significantly correlated with dyslipidemia, which is correlated with insulin resistance [3]. The TG/HDL-C concentration ratio and the combination of EW and ET (EWET) are good surrogate estimates of insulin resistance, as is fasting plasma insulin concentration, and are as effective as the ATP III MetSyn criteria in identifying insulin-resistant individuals [12,14-16]. Therefore, TG/HDL-C ratio ≥3.0 and EWET have been included in this analysis as another simple approach with which to identify overweight/obese individuals at increased CVD risk who would benefit from more aggressive treatment.

Although the existing clinical criteria for MetSyn can lead to substantially different estimated prevalence and burden of MetSyn within a population [18-22], the question remains if these clinical criteria identify similar or different individuals. Several studies have used 2 of these clinical criteria to compare the cross-sectional prevalence of MetSyn within the US population [18-22]. Currently, only a few studies have used more than 2 clinical criteria for MetSyn to identify and compare individuals with MetSyn [23-25]. The primary objective of this analysis was to determine to what extent the clinical criteria for MetSyn, TG/HDL-C ratio ≥3.0, and EWET identify similar or different women enrolled in a weight loss trial.

Regardless of the clinical criteria for MetSyn, weight reduction has been proposed as the primary target of treatment because of its beneficial effects on metabolic

Table 2
Anthropometric and metabolic characteristics of participants identified with MetSyn

Variable	WHO (n = 56)	EGIR (n = 42)	ATP III (n = 81)	IDF (n = 83)	TG/HDL-C (n = 79)	EWET (n = 83)
Age (y)	42 ± 6	42 ± 6	43 ± 5	43.5 ± 5	42 ± 6	42.5 ± 5.0
Weight (kg)	93.6 ± 11.7	93.0 ± 12.3	89.5 ± 13.6	89.0 ± 13.8	87.8 ± 13.1	89.8 ± 13.6
BMI (kg/m^2)*	34.8 ± 3.3^{a}	34.3 ± 3.3^{a,b}	32.9 ± 3.7^{a,b}	32.7 ± 3.8^{a,b}	32.6 ± 3.8^{b}	33.0 ± 3.7^{a,b}
WHR	0.89 ± 0.06	0.89 ± 0.06	0.87 ± 0.07	0.87 ± 0.07	0.87 ± 0.07	0.88 ± 0.07
WC (cm)	104 ± 9	104 ± 9	100 ± 9	100 ± 9	99 ± 9	101 ± 9
TG (mg/dL)	186 ± 113	206 ± 118	185 ± 102	184 ± 102	210 ± 85	206 ± 83
HDL-C (mg/dL)	44 ± 8	42 ± 7	44 ± 7	44 ± 7	44 ± 8	46 ± 9
FPG (mg/dL)	104 ± 26	107 ± 28	102 ± 22	102 ± 22	97 ± 15	96 ± 14
FPI (μU/mL)*	19 ± 7^{a}	19 ± 8^{a}	13 ± 8^{b}	13 ± 8^{b}	14 ± 8^{b}	14 ± 8^{b}
SBP (mm Hg)	121 ± 12	121 ± 13	124 ± 14	124 ± 14	120 19.9 ± 14	121 ± 12
DBP (mm Hg)	78 ± 8	78 ± 9	80 ± 10	80 ± 10	77 ± 10	77 ± 9

Values are mean ± standard deviation. [a,b]Values with different superscript letters within a row are significantly different ($P < .05$). FPI indicates fasting plasma insulin; SBP, systolic blood pressure; DBP, diastolic blood pressure.

* Significant difference was observed between MetSyn clinical criteria.

abnormalities [26,27]. The Obesity Education Initiative guidelines state that the initial goal for a weight loss intervention should be a 7% to 10% reduction in body weight within 6 months of initiating an intervention [27]. Therefore, a secondary objective was to examine the impact of 7% weight reduction on MetSyn status.

2. Materials and methods

2.1. Participants

Secondary analyses were conducted using data from a weight loss study originally designed to compare 4 popular weight loss diets [28]. Participants, recruited primarily through newspaper advertisements, were invited to enroll if they were 25 to 50 years of age, were premenopausal (defined as having a regular menstrual cycle), had a BMI of 27 to 40 kg/m^2, were nonsmokers, had stable weight over the previous 2 months, and were stable for ≥3 months on their medications. Women were excluded if they (*a*) had self-reported hypertension (except for those stable on antihypertension medications); type 1 or 2 DM; heart, renal, or liver disease; cancer or active neoplasms; or hyperthyroidism unless treated and under control; (*b*) were taking any medications known to affect weight/energy expenditure or lipid metabolism; (*c*) had alcohol intake ≥3 drinks a day; or (*d*) were lactating, pregnant, or planning to become pregnant within the next year. All participants provided written informed consent. The study was approved by the Stanford University Human Subjects Committee.

2.2. Intervention

After baseline data collection, participants were randomly assigned to follow one of 4 diet books: *Dr Atkins' New Diet Revolution* [29], *The LEARN Program for Weight Management* [30], *Eat More Weigh Less* [31], or *Enter the Zone: A Dietary Road Map* [32]. Each diet group attended eight 1-hour evening classes once per week over 8 weeks and was assigned approximately one eighth of their respective books per class. A registered dietitian led the classes and the review of assigned material. Participants were instructed to master their assigned diet by the end of the 8-week class and then to continue following their diets on their own for the subsequent 10 months.

2.3. Clinical measurements

Clinical measurements were obtained at baseline and at 2, 6, and 12 months. For these post hoc exploratory analyses, only baseline and 6-month data were used because of the Obesity Education Initiative guidelines for what constitutes a successful weight loss intervention (7%-10% reduction in body weight within 6 months of initiating an intervention) [27]. Body weight was measured in light clothing to the nearest 0.1 kg using a calibrated clinical scale. Standing height was measured to the nearest millimeter using a standard wall-mounted stadiometer. Waist and hip circumferences were measured to the nearest millimeter by standard procedures using an anthropometric measuring tape [33]. After 5 minutes of quiet rest, resting blood pressure was assessed 3 times at 2-minute intervals, the initial reading was discarded, and the last 2 readings were averaged [34].

Blood samples were collected after a 12-hour fast. Blood sampling and processing were conducted at the Stanford University Hospital General Clinical Research Center. Plasma TG (with subtraction of a free glycerol blank) was measured by enzymatic procedures using established methods [35]. High-density lipoprotein cholesterol was measured by liquid selective detergent followed by enzymatic determination of cholesterol [36,37]. Plasma glucose concentration was measured using a modification of the glucose oxidase/peroxidase method [38,39]. Plasma insulin concentration was measured by radioimmunoassay [40].

2.4. Metabolic syndrome diagnosis

Based on clinical measures obtained in this investigation, MetSyn was diagnosed using the clinical criteria presented in Table 1. For the WHO clinical criteria, insulin resistance was

Table 3
Agreement and disagreements between clinical criteria for MetSyn

Groups	κ (% agreement)	κ 95% CI	MetSyn positive	MetSyn negative	Disagreement (%)
Comparison groups with different insulin resistance requirement					
WHO–IDF	0.39 (75.9)	0.26-0.51	WHO	IDF	31.5
			IDF	WHO	55.4
WHO–TG/HDL-C	0.39 (76.6)	0.27-0.51	WHO	TG/HDL-C	33.3
			TG/HDL-C	WHO	54.4
WHO–ATP III	0.40 (76.6)	0.28-0.52	WHO	ATP III	31.5
			ATP III	WHO	54.3
WHO–EWET	0.37 (75.1)	0.24-0.49	WHO	EWET	33.3
			EWET	WHO	56.6
EGIR–TG/HDL-C	0.40 (78.2)	0.28-0.52	EGIR	TG/HDL-C	23.8
			TG/HDL-C	EGIR	59.5
EGIR–IDF	0.42 (78.2)	0.30-0.54	EGIR	IDF	19.0
			IDF	EGIR	59.0
EGIR–ATP III	0.43 (78.9)	0.31-0.55	EGIR	ATP III	19.05
			ATP III	EGIR	58.0
EGIR–EWET	0.36 (75.9)	0.23-0.48	EGIR	EWET	26.2
			EWET	EGIR	62.7
Comparison groups with similar insulin resistance requirement					
TG/HDL-C–ATP III	0.59 (82.4)	0.48-0.69	TG/HDL-C	ATP III	27.9
			ATP III	TG/HDL-C	29.6
TG/HDL-C–IDF	0.59 (82.4)	0.48-0.69	TG/HDL-C	IDF	26.6
			IDF	TG/HDL-C	30.1
EWET–ATP III	0.55 (80.8)	0.44-0.66	EWET	ATP III	31.3
			ATP III	EWET	29.6
EWET–IDF	0.54 (80.1)	0.43-0.65	EWET	IDF	31.3
			IDF	EWET	31.3
WHO–EGIR	0.85 (95.4)	0.76-0.93	WHO	EGIR	22.2
			EGIR	WHO	0
ATP III–IDF	0.98 (99.2)	0.96-1.0	ATP III	IDF	0
			IDF	ATP III	2.4

Agreement is given in κ statistics (percentile). The WHO and EGIR both required some measure of insulin resistance; and ATP III, IDF, TG/HDL-C, and EWET did not require any measure of insulin resistance. Only participants (n = 99) that met the criteria of at least one of the MetSyn clinical criteria were included. Within each comparison group, *MetSyn positive* refers to the individuals identified as having MetSyn using one of the clinical criteria; and *MetSyn negative* refers to the individuals identified as not having MetSyn using the other clinical criteria.

defined as fasting plasma insulin >75th of the study population [41,42]. With respect to the IDF clinical criteria of MetSyn, the Europid waist circumference cutoff of 80 cm was used to determine obesity status in all participants (ie, the different ethnic-specific cutoffs for Japanese vs South Asian women could not be used because demographic data did not distinguish these 2 Asian populations). The TG/HDL-C ratio was calculated for all participants, and a cutoff was set at ≥3.0. In all participants, EWET was defined as waist circumference ≥88 cm and TG ≥129 mg/dL.

2.5. Statistical analysis

Means ± standard deviations and proportions of participants identified with the various clinical criteria for MetSyn were calculated. The agreements between the clinical criteria were determined using κ statistics. Levels of agreement were considered slight, fair, moderate, substantial, and almost perfect, with κ = 0.00 to 0.20, 0.21 to 0.40, 0.41 to 0.60, 0.61 to 0.80, and 0.81 to 1.00, respectively [43]. Differences in baseline risk factor levels between participants identified by the different clinical criteria for MetSyn were compared using a general linear model, and Scheffe post hoc analysis was used to further explore significant findings. Differences in the impact of 7% weight reduction on MetSyn status were compared with χ^2 statistics (these analyses do not meet the assumptions of independent samples but were conducted for descriptive purposes). All analyses were performed using SAS version 9.1 (SAS, Cary, NC).

3. Results

Of the 311 women enrolled in the study, blood sample results were not available at either baseline or 6 months for 55 women. Therefore, 256 (82%) women were included in these secondary analyses. The race/ethnicity breakdown was 71% white, 11% Hispanic, 10% Asian/Pacific Islander, 6% African American, and 3% other. Of the 256 women, 157 did not meet any of the clinical criteria for MetSyn, whereas 99 met at least one of the clinical criteria for MetSyn. Anthropometric and metabolic characteristics of participants identified with MetSyn are depicted in Table 2. It should be noted that substantially more individuals were identified as

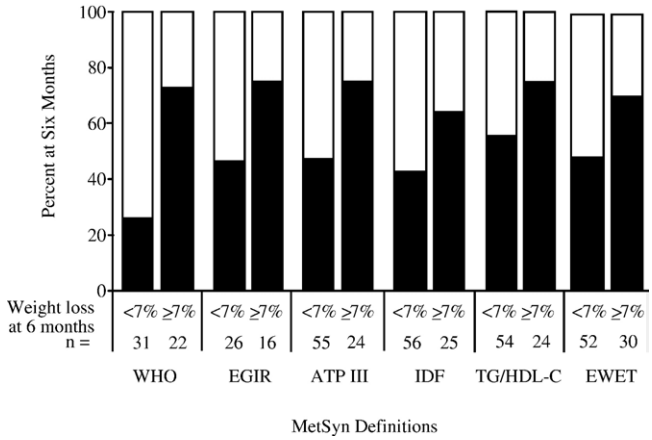

Fig. 1. Effect of weight loss on MetSyn status at 6 months. Metabolic syndrome criteria after 6 months: □, still meets criteria; ■, no longer meets criteria. *Includes women who gained weight. Eighty-three of the 256 participants lost ≥7% of baseline body weight. Metabolic syndrome could not be diagnosed in 3 participants (WHO, n = 3; ATP III and IDF, n = 2) at the 6-month time point because of missing blood sample. Within-group differences were statistically (χ^2 test) significant at $P < .01$.

being at high risk by the ATP III, IDF, TG/HDL-C, and EWET criteria; and with the exception of BMI and plasma insulin concentrations, the groups were not different in CVD risk factors.

According to EGIR, WHO, ATP III, and IDF clinical criteria, 16.1%, 20.7%, 31.0%, and 31.8% of the participants were identified with MetSyn, respectively, with 30.3% and 31.8% having TG/HDL-C ratio ≥3.0 and EWET, respectively. The agreement between the clinical criteria in identifying participants with or without MetSyn was between 75.1% and 99.2% (Table 3). The highest and lowest levels of agreement were observed between ATP III and IDF ($\kappa = 0.99$; 95% confidence interval [CI], 0.96-1.0) and WHO and IDF ($\kappa = 0.39$; 95% CI, 0.26-0.51), respectively. Specific disagreement for each pair comparison is provided in Table 3. For example, among participants identified with MetSyn using the WHO clinical criteria, 31.5% were not identified by the IDF clinical criteria; and conversely, among those identified using the IDF clinical criteria, 55.4% were not identified by the WHO clinical criteria. The primary disagreement between WHO and IDF was due to differences in insulin resistance requirement. There was a moderate level of agreement between participants identified with elevated TG/HDL-C ratio and EWET and those identified as having MetSyn by the different clinical criteria.

The 4 organizations' clinical criteria for MetSyn used different cutoffs for certain components. Within our cohort, the prevalence of obesity as defined by the 4 organizations' clinical criteria ranged between 76.3% and 100%. Similarly, within the entire cohort, dyslipidemia, hyperglycemia, and elevated blood pressure ranged between 27.6% and 55.6%, 6.9% and 18.0%, and 5.4% and 15.7%, respectively. In individuals identified with MetSyn by WHO and EGIR, the most common metabolic abnormality was hyperinsulinemia. In those identified with ATP III and IDF MetSyn, dyslipidemia was the most common metabolic abnormality. Overall, obesity was the most common metabolic abnormality within all MetSyn clinical criteria, which is not surprising because participant inclusion criteria require a BMI of 27 to 40 kg/m^2. In individuals identified with MetSyn, hyperglycemia and high blood pressure ranged between 20.4% and 43.4% and between 11.1% and 39.5%, respectively.

The effect of weight loss on MetSyn status is depicted in Fig. 1. Participants on average lost 3.9 ± 5.7 kg after 6 months on their assigned diets. This represents a 4.5% ± 6.5% reduction in their baseline body weight. Of the participants that initially met the various criteria for MetSyn and subsequently lost ≥7% of their baseline body weight in 6 months, 64.0% to 75.0% no longer met the criteria for this diagnosis. However, among participants who initially met the criteria for MetSyn and at 6 months had lost <7% of their baseline body weight, only 25.8% to 55.6% no longer met the criteria for MetSyn. Within-group differences were statistically significant ($P < .01$). Of those assigned to the different diet treatment arms who met the MetSyn criteria at baseline, 22.1% to 72.7% (Atkins), 50.0% to 62.5% (LEARN), 20.0% to 54.6% (Ornish), and 43.8% to 54.6% (Zone), depending on the clinical criteria, were able to change their MetSyn status from positive to negative after 6 months of being on their assigned diets.

4. Discussion

Among these overweight/obese women enrolled in a weight loss study, the estimated prevalence of MetSyn doubled depending on the clinical criteria used. The clinical criteria similarly classified 77% to 99% of the participants as either having or not having MetSyn. Nonetheless, up to 23% of the participants were classified differently by the clinical criteria. Triglyceride/HDL-C ratio ≥3.0 and EWET moderately agreed with the other clinical criteria, and both appear to be a reasonably effective and simplified measure for identifying participants at increased CVD risk. Despite differences in these clinical criteria, ≥7% body weight reduction was an effective strategy for changing MetSyn status.

In 2007, de Simone et al [24] examined similarities and differences between the MetSyn clinical criteria proposed by WHO, ATP III, and IDF in identifying American Indians with MetSyn. Similar to our results, they reported that the IDF clinical criteria for MetSyn identified more individuals as having MetSyn than the other clinical criteria. Their reported levels of agreement between WHO and IDF (κ = 0.50) and between WHO and ATP III (κ = 0.59) were slightly higher than what was observed in the present analysis. However, their reported agreement between ATP III and IDF (κ = 0.77) was lower than what we observed. It is possible that differences in the observed agreement levels

between the present analysis and the study of de Simone et al could be attributed to differences in study participant population and the inclusion of individuals with type 2 DM by de Simon and colleagues in their study.

Currently, all 4 clinical criteria for MetSyn are used in the medical literature either to define eligibility criteria to participate in a particular study or to make inferences regarding MetSyn and disease risk [23,44-46]. However, as our results show, the clinical criteria used for diagnosis may influence the prevalence of MetSyn and therefore could potentially impact research findings. In the sense that if different groups of investigators recruit participants with MetSyn but use different clinical criteria, then the comparisons of the 2 studies may be problematic. It may appear that similar populations are being compared because in both cases the investigators have defined their participants as meeting the MetSyn criteria. However, if different clinical criteria were used, then the populations may not be as similar as might be assumed. The significance would be that there might appear to be more heterogeneity among studies than is actually the case.

Clearly, some of the clinical criteria yield similar results with respect to identifying similar participants. For example, in the present cohort, the highest agreement level was found between ATP III and IDF, which use the same components and identical cutoffs to define MetSyn with the exception of a lower waist circumference cutoff for IDF. The IDF clinical criteria require the presence of abdominal obesity (ie, large waist circumference), whereas ATP III considers abdominal obesity one of 5 equally weighted metabolic abnormalities. However, this makes little practical difference as can be seen by the 99% agreement in diagnosis observed in our study. In general, the highest disagreement was found between clinical criteria that required the presence of insulin resistance (WHO and EGIR) and those that did not (ATP III and IDF). If the purpose for the clinical criteria for MetSyn is to help clinicians identify overweight/obese individuals at increased risk, ATP III, IDF, TG/HDL-C ratio $\geq$3.0, and EWET all identify similar numbers of at-risk individuals with similar risk factor levels. Among these, the TG/HDL-C ratio and EWET have the advantage of being easier and potentially less expensive to determine because they only require a lipid panel and anthropometric measure.

Approximately 32% of the participants involved in this study were able to lose $\geq$7% of their baseline body weight in 6 months. Regardless of the clinical criteria used, most participants identified with MetSyn at baseline who lost $\geq$7% of their baseline body weight in 6 months changed their MetSyn status from positive to negative. Weight reduction has been shown to significantly improve all MetSyn components [4,10].

A strength of this analysis was its longitudinal design that allowed us to examine the effect of weight reduction on MetSyn status. However, because the primary study was not designed to investigate similarities or differences in the clinical criteria for MetSyn, we did not have complete information for all 4 clinical criteria. With respect to the IDF clinical criteria, we lacked information on Asian subgroups and were unable to use ethnic-specific waist circumference cutoffs, which could have led to an overestimation of MetSyn prevalence in participants of Japanese descent. However, only 10% of our entire population was Asian; and therefore, only a subset of this 10% could have been Japanese, suggesting that the potential overestimation was minor. With respect to the WHO clinical criteria, the operational definition of insulin resistance requires a hyperinsulinemic euglycemic clamp procedure, a technique that is not feasible in clinical or epidemiological research settings and that was not performed in our study. We used fasting plasma insulin as a surrogate measure of insulin resistance [41]. We also did not assess the microalbuminuria level in our participants, which is a factor for the WHO classification. High microalbuminuria levels have been associated with endothelial dysfunction and increased risk for CVD [44,47]. However, some researchers have questioned the association between microalbuminuria and insulin resistance and its inclusion as a MetSyn criterion [8]. In addition, in our study of overweight/obese but generally healthy premenopausal women, the prevalence of microalbuminuria was likely very low and should not have had a substantial impact on WHO-defined MetSyn prevalence. Other than these exceptions, we had complete data on the extensive set of criteria for the various MetSyn criteria for all 256 participants in this analysis. Another study limitation is that menstrual cycle timing was not taken into consideration for blood sampling, which could have increased within-person variability in the blood lipid analysis. In addition, participant's menopausal status was assessed only at baseline. Therefore, it is possible that a few of the older participants could have been in transition from pre- to perimenopausal status over the 6 months, which may have had an impact on hormone levels and subsequently on blood lipid levels [48]. Finally, it should also be noted that the baseline MetSyn prevalence rates would have been somewhat higher if the study sample had not excluded those who were on lipid-lowering medications or those who were hypertensive and not stable on antihypertensive medications.

Individuals diagnosed with MetSyn are at an increased risk of developing CVD and type 2 DM [6,22,23,41,49,50]. This association is not surprising because the individual components of MetSyn are mechanistically linked with both diseases; and when these metabolic abnormalities cluster together, they confer an increased risk for CVD and type 2 DM [51-54]. The question remains if the clinical treatment of metabolic abnormalities are different in the presence or absence of MetSyn, and the answer would appear to be no. Currently, physicians treat the individual metabolic abnormalities of MetSyn, not the MetSyn itself; and they tend to treat them more aggressively when multiple abnormalities are identified, regardless if the individual has MetSyn or not. In this context, the potential clinical merit of both the TG/HDL-C ratio and EWET seems to deserve consideration;

they are simpler to assess than the 4 clinical criteria for MetSyn and identify a similar number of overweight/obese individuals at increased CVD risk. However, if the benefit of MetSyn diagnosis is largely for research purposes, then discrepancies across the clinical criteria will make it difficult to compare results from studies that use different clinical criteria. Therefore, there are multiple reasons to question the clinical or pedagogical utility of MetSyn [55]. Weight loss has been shown to be an effective strategy for improving all 5 of the common metabolic abnormalities used to diagnosis MetSyn [4,10]. In conclusion, although research is still needed to define the optimal clinical criteria for MetSyn diagnosis, more clinical and research effort should be geared toward developing successful weight loss strategies.

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