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APPLICATION OF THE AACE/ACE ADVANCED FRAMEWORK FOR THE DIAGNOSIS OF OBESITY AND CARDIOMETABOLIC DISEASE STAGING IN A GENERAL POPULATION FROM THREE REGIONS OF VENEZUELA: THE VEMSOLS STUDY RESULTS.

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Running Title: Obesity in Venezuela

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Abstract

Objective: To determine the prevalence of obesity according to the AACE/ACE framework based on a complications-centric model with further application of the Cardiometabolic Disease Staging (CMDS) system in Venezuelan population.

Methods: 1,320 adults were randomly selected from 3 regions. AACE/ACE framework definitions: overweight: body mass index (BMI) 25 to 29.9 kg/m^2 and no obesity-related complications (ORC); obesity stage 0: BMI ≥ 30 and no ORC; stage 1: BMI ≥ 25 and one or more mild-to-moderate ORC; and stage 2: BMI ≥ 25 and one or more severe ORC. CMDS definitions: stage 0: no metabolic syndrome (MS) components; stage 1: 1-2 MS components without impaired fasting glucose [IFG]; stage 2: IFG, or ≥ 3 MS components but without IFG; stage 3: IFG and MS; and stage 4: type-2 diabetes or cardiovascular disease.

Results: Mean age was 44.8±0.4 years and 68.5% were females. The prevalence of obesity according to the AACE/ACE framework was 63.5%: overweight 3.0% (95% CI: 2.1 - 3.9); obesity stage 0: 0.1% (0.07 - 0.27); obesity stage 1: 26.6% (24.2 – 29.0); and obesity stage 2: 36.4% (33.8 - 39.0). Most of the subjects with BMI < 25 were CMDS 0 or 1. In those with BMI ≥ 25, only 4.6% were CMDS 0. The prevalence of obesity according to the WHO (BMI ≥ 30) was 29.3% (24.7 - 33.7).

Conclusion: In a general population study, applying the AACE/ACE framework for obesity and CMDS increased the detection of ORC and therefore higher risk subjects compared to classic anthropometric measurements.

Key Words: Obesity; Overweight; Prevalence; Framework; Body Fat; Venezuela.

Word counting: 3,133

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Introduction

Excess body fat increases the likelihood of diabetes, hypertension, coronary heart disease, stroke, certain cancers, obstructive sleep apnea, and osteoarthritis.[1,2] Overweight and obesity, represented by increased body mass index (BMI) 25-29.9 kg/m^2 and ≥30 kg/m^2, respectively, were the sixth leading global disease burden, accounting for 3.4 million deaths per year and 3.8% of global disability-adjusted life years (DALY; sum of years lived with disability and years of life lost) in 2013.[3] In Latin America (LA), BMI values have increased 1.1 kg/m^2 in men and 0.7 kg/m^2 in women, per decade, from 1980 to 2008;[4] placing an increased BMI as the third regional cause of disease burden.[3] A national population survey to investigate the prevalence of overweight and obesity has not been performed in Venezuela.[5] Based on published regional and sub-national studies (7) in 3,368 subjects,[6] the weighted prevalence - according to the size sample of each study included- of obesity (BMI ≥30 kg/m^2) in Venezuela was calculated at 26.3%.

The new perspective of obesity as a chronic, complex disease[7] imposes a new clinical and epidemiological approach to patients with unhealthy accumulation, distribution, and function of fat mass. The current definition of obesity is based on the BMI.[8] However, accumulation of excess body fat represents a continuum that includes overweight individuals with a lesser degree of excessive adiposity that can also adversely impact health as well as metabolically healthy individuals with obesity.[9] The phenotypic and metabolic spectrum of obesity is influenced by race, ethnicity, and body type,[9] demanding a refinement of BMI cut-offs to diagnose obesity in different populations, and the need for additional measures of adiposity, such as waist circumference (WC) or body fat percentage.[10] A complete cardiometabolic health diagnosis does not only depend upon BMI value. The BMI as isolated both diagnosis and clinical decision-

making tool can underperforms, whereas a complications centric approach will provide a better understanding of impact of increased body fat on health. [7] In addressing this issue, the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE),[11] in 2014, asserted that BMI *per se* does not reflect the impact of weight gain on the health or wellbeing of the individual. Consequently, AACE/ACE proposed a medical definition of obesity incorporating not only the continued use of BMI, but also other physical assessments including the presence and severity of obesity-related complications (ORC) to reflect the health impact of adiposity for individual patients (AACE/ACE framework).[11,12] Of note, the prevalence rates for obesity and ORC according to this AACE/ACE framework are unknown.

The objective of this study was to determine the prevalence of obesity and ORC according to the AACE/ACE framework in five populations in the Venezuelan Metabolic Syndrome, Obesity and Lifestyle Study (VEMSOLS), as well as assessing risks for each obesity stage using the Cardiometabolic Disease Staging (CMDS) system. Furthermore, these results were compared with data using other definitions, including the World Health Organization (WHO) BMI cut-off points,[13] fat mass percentage,[10] and abdominal obesity with cut-offs adapted to Latin America.[14]

Material and methods

Population studied

The study was designed to evaluate five populations in three regions from Venezuela: Palavecino Municipality (urban) in Lara State from the Western region; Ejido (urban) and Rangel (Páramo area, rural) Municipalities in Merida State from the Andes region; Catia Municipality (urban) in Vargas state and Sucre Municipality (urban) in Capital

District, both from the Capital region. During the years 2006 to 2010, a total of 1,320 mostly mixed subjects aged 20 or older that lived in their houses for at least six months were selected by multistage stratified random sampling of the five studied populations. Pregnant women and participants unable to stand and/or verbally communicate were excluded. The study protocol was approved by the Council of Scientific, Humanistic and Technological Development (CDCHT) of the Universidad Centro-Occidental "Lisandro Alvarado" in Venezuela.

Clinical and biochemical data

All subjects were evaluated in their home or in a nearby health center by a trained health care team according to a standardized protocol. Each home was visited twice. In the first visit, the participants received information about the study and the written informed consent was obtained. Demographic and clinical information was obtained using a standardized questionnaire. Blood pressure (BP) was measured twice in the right arm supported to the heart level, in sitting position, after five minutes of rest, using a calibrated aneroid sphygmomanometer. Weight was measured with the fewest clothes possible, without shoes, using a calibrated scale. Height was measured using a metric tape on the wall. BMI was calculated as weight (kg)/height $(m)^2$. Body fat percent (BF %) by leg bioimpedance (Tanita®, Tanita Corp., Tokyo, Japan) was obtained from 529 participants. Waist circumference (WC) was measured at the iliac crest, in a plane horizontal to the floor at the end of expiration.

In the second visit, blood samples were drawn after 12 hours of overnight fasting. The samples were centrifuged for 15 minutes at 3000 rpm within 30-40 minutes after collection, transported on dry ice to the central laboratory, and properly stored (-40°C) until analysis. Glucose plasma concentration,[15] total cholesterol,[16] triglycerides (TG),[17] low density lipoprotein of cholesterol (LDL-c), and high density lipoprotein of cholesterol (HDL-c),[18] were determinate by enzymatic colorimetric methods.

Categorization of variables

Obesity prevalence was estimated using five different definitions and staging systems. First, obesity and overweight were defined according to the AACE/ACE framework[11,12] and included 4 categories: overweight - BMI 25 to 29.9 kg/m^2 and no ORC; obesity stage 0 - BMI ≥ 30 kg/m^2 and no ORC; obesity stage 1 - BMI ≥ 25 kg/m^2 and presence of one or more mild-to-moderate ORC; and obesity stage 2 - BMI ≥ 25 kg/m^2 and presence of one or more severe ORC. ORC included the presence or absence of cardiometabolic risk factors, which were staged for degree of increasing severity using CMDS (Table 1).[18]

Second, CMDS[19] was evaluated in subjects with BMI ≥ 25 kg/m^2 compared with subjects with BMI < 25 kg/m^2. CMDS defined populations at progressively increasing risk for T2D, cardiovascular disease mortality, and all-cause mortality. CMDS can be used to further stratify risk for T2D and cardiovascular disease (Table 1). Third, WHO-BMI[20] overweight and obesity definitions were applied and correlated with cardiometabolic risk factors: normal weight, BMI < 25 kg/m^2; overweight, BMI 25 to < 30 kg/m^2; and obesity, BMI ≥ 30 kg/m^2. Fourth, abdominal obesity was established according to proposed Latin American cut-offs for WC ≥ 94 cm in men and ≥ 90 cm in women.[14] Finally, an obesity definition using percentage body fat (BF %) from bioimpedance analysis was established according to WHO as >25% in men and >35% in women.[21]

Statistical Analysis

All calculations were performed using SPSS 20 program (IBM corp, Released 2011;

Armonk, NY, USA). Normality was assessed using Kolmogorov-Smirnov and Q-Q plots and was initially performed for each variable. Data for continuous variables were presented as mean and standard deviation (SD), except blood glucose, which was not normally distributed, and was therefore presented as median and interquartile range (IR). Differences between mean values were assessed by analysis of variance (ANOVA) and then adjusted for multiple comparisons using the Tukey post hoc test. Difference between medians of blood glucose was evaluated by the Mann-Whitney U test. Proportions were presented as percent and 95% confidence intervals (95% CI). Chi square testing was applied to compare different frequencies. A p-value of < 0.05 was considered to be statistically significant. Logistic regression was used to calculate age as a risk factor related with obesity.

Results

Subjects characteristics

Approximately two thirds of the sample was female. Both genders had similar age and BMI. Men had higher weight, height, and WC than women, but lower BF% (Table 2).

Prevalence of obesity according to AACE/ACE framework

The prevalence of obesity (stages 0-2) according to the AACE/ACE framework was 63.5% (Table 2). Only one woman who had obesity (BMI $\geq$ 30 kg/m^2) and only 3% of the overweight sample (BMI $\geq$ 25 to 29.9 kg/m^2) were without ORC (i.e., AACE Stage 0). Most of the patients with BMI $\geq$ 25 kg/m^2 had complications: mild-moderate ORC stage 1 (26.6%); severe ORC stage 2 (36.4%).

When CMDS was used to assess metabolic health and cardiometabolic risk, most (79%) of the subjects with BMI <25 kg/m^2 had CMDS stage 0 or 1 (Table 3A). In contrast, most of the subjects with BMI from 25 to 29.9 kg/m^2 (84.2%) and BMI $\geq$ 30 kg/m^2

(89.8%) were characterized by greater degrees of cardiometabolic risk with CMDS 1 to 3. When CDS was dichotomized in metabolically healthy (stage 0) and metabolically unhealthy (stages 1 – 3) (Figure 1), the proportion of subjects who were metabolically unhealthy increased in every category of BMI, from 73.1% in those with BMI <25 kg/m^2, to 92% in BMI 25 to 29.9 kg/m^2, to 99.7% in BMI ≥ 30 kg/m^2.

Prevalence of obesity by other definitions

According to the WHO classification of obesity, two thirds of subjects had overweight or obesity (Table 4-A). Half of the subjects had excess adiposity by BF% and abdominal obesity by increased waist circumference, although these rates were somewhat higher in men than women (Table 4-B, C). The prevalence of obesity and overweight, according to the WHO, varied with age, being more prevalent in the middle-aged groups ($p < 0.05$) (Table 5). Mean values of all cardiometabolic risk factors were increased as a function of the WHO-BMI classification, with the exception of blood glucose, which was not influenced by BMI category (Table 3B). Lipid values, except HDL-c and total cholesterol, were similar between subjects with overweight and obesity.

The prevalence rates of obesity according to all definitions are provided in Figure 2 and demonstrate how the new AACE/ACE framework improves the detection of subjects at risk when compared with other definitions.

Discussion

The new AACE/ACE diagnostic framework for obesity allows integrative evaluation of patients using both anthropometric measures to confirm excess adiposity and clinical measures involving the detection and staging of ORCs, which increases the identification of subjects at risk in a general population study of Venezuela. The

application of this definition matched the number of subjects categorized as obese according to the WHO definition but detected a surprisingly high number of subjects with ORC at relatively lower levels of fat mass (BMI <30 kg/m^2). Increased BMI was more frequent in middle age subjects, and blood pressure increased in each category of nutritional state, though lipid values, with the exception of HDL-c and total cholesterol, were similar in subjects with overweight or obesity. A particular characteristic observed in this population was that BMI-defined weight status did not affect blood glucose concentration.

Globally, the age-standardized mean BMI of adults is increasing 0.63 kg/m^2 per decade (0.53-0.73) in men and 0.59 kg/m^2 per decade (0.49-0.70) in women.[22] Therefore, with this projection and current screening and diagnostic strategies, it will be unlikely that the goal proposed to halt the rise of non-communicable diseases for 2025 can be reached.[23] The WHO had estimated that by 2014, more than half billion of subjects with obesity, and the prevalence calculated in the Region of the Americas (27%) was similar to the results in the present study (29.3%).[24]

These discouraging figures result from the exclusive use of BMI to detect obesity – a BMI-centric model - which impairs public health strategies and emerging personalized care by underestimating the number of people with excess body fat (not to mention whether the abnormal adiposity is biologically relevant). For example, in the present study, 16.3% less subjects were categorized with obesity using BMI ≥30 kg/m^2 compared with %BF-defined obesity. Similar results has been demonstrated in the U.S. population according to National Health and Nutrition Examination Survey (NHANES) data, were BMI-Obesity definition underestimate 29.2% of men and 31.4% of women with obesity detected by %BF-definition.[25] An evaluation of 1,375 Venezuelan patients aged ≥18 years also reported that a BMI cutoff of ≥30 kg/m^2 misses 21% of

people with excess adiposity determined by bioelectrical impedance analysis.[26] The best BMI cutoff to categorize obesity based on BF% in the Venezuelan population was 27.5 kg/m^2, with a sensitivity of 89.3% (95% CI, 87–91) and a specificity of 85.4% (95% CI, 81–89).[26] Similar BMI cutoffs were found in 750 subjects in a general population sample from three of the regions included in the present study. Therefore, it should be noted that in Venezuela and other populations, many people without obesity would be re-classified as subjects with obesity based on direct measurements of body adiposity. Likewise, 22.7% more individuals were detected with central obesity using waist circumference cutoffs specific for LA, compared with using BMI alone. These findings in tandem reinforce the recommendation to complement the BMI-centric obesity with other anthropometrics to better delineate individual cardiometabolic risk.[10]

The new, advanced AACE/ACE framework to define obesity as a chronic, complex disease based on a complications-centric system for those with BMI ≥ 25 kg/m optimizes the public health model even further by incorporating biological relevance.[11,12] Thus, stepwise application of the AACE/ACE framework[11,12] includes: step 1 - screening anthropometric measures to assess body mass classifications, with transcultural adjustments as needed; step 2 – systematic evaluation of complications using an explicit checklist; step 3 - disease staging as stage 0 with no complications, stage 1 with mild-moderate complications, and stage 2 with severe complications; and step 4 – practical implementation of the AACE/ACE obesity algorithm for selecting modality and intensity of therapy.[12] This algorithm flows to three broad categories of therapy based on complication-centric staging: lifestyle therapy, including behavioral counseling and structured programs; pharmaceutical therapy; and bariatric procedures (nonsurgical and surgical). In the Venezuelan cohort, obesity staging goes beyond BMI

to indicate the impact that excess adiposity has on the health of individuals, and to identify patients requiring more aggressive intervention over a broad range of BMI.

CMDS[19,27], was also used to risk stratify individuals for future development of diabetes and cardiovascular disease. These data were consistent with high degrees of risk in both overweight and obesity. The Venezuelan population was characterized by low prevalence of overweight or obesity patients exhibiting no Metabolic Syndrome traits, who are categorized as CMDS Stage 0. These patients have been referred to as the metabolically healthy obesity profile, and comprised only 8% of the overweight and 0.3% of the subjects with obesity. These prevalence rates are much lower than has been observed in other countries. In the US, approximately 15% of adults with overweight or obesity are free of cardiometabolic disease risk factors, and this rate has remained stable from 1988 to 2014. [28,29] Prevalence rates of the metabolically healthy obese vary among European countries, with an average value that also approximates 15%.[30] On the other hand, both patients with overweight and obesity in Venezuela have high rates of CMDS Stage 1 (47.1% and 39.1% respectively) and high rates of CMDS Stage 2-3 in patients with Metabolic Syndrome and/or prediabetes (37.1% and 40.7% respectively). When compared to the US adults with overweight or obesity, the prevalence of individuals with 3 or more risk factors (CMDS Stage 2-3) increased from 16.4% to 22.4% over the years 1988 to 2014 commensurate with a decline in those with 1 or 2 risk factors (CMDS Stage 1) from 69.6% to 62.4%.[28] Two salient points emerge from these data. First, overweight and obesity carries with it a high burden of cardiometabolic disease risk in the Venezuelan population. Second, BMI alone is a poor predictor of risk for diabetes and cardiovascular disease. Cardiometabolic disease risk as reflected by CMDS scores afflicted high numbers of individuals with either overweight or obesity, and even considerable numbers of lean

individuals. For this reason, it is clear the risk stratification independent of BMI is needed to assess risk for diabetes and cardiovascular disease in order to target high risk patients for weight loss therapy.[19,27] Given the high prevalence of overweight and obesity, CMDS and the AACE/ACE staging paradigm for ORCs could be used as a guide to a rational strategy for diabetes prevention based on benefit, risk, and cost effectiveness.

Several limitations of this study deserve mention. First, the AACE/ACE framework included many of the specified weight-related complications that were not formally screened or evaluated. However, this would only have had an effect of amplifying our findings that a BMI-centric protocol underestimated the clinical relevance and adverse impact of excess weight. Second, this study was retrospective in nature, and prospective observational studies would add further confirmation of these findings. A specific strength of this study is the application of a U.S. developed obesity framework to a Latin American country with a distinctly different ethno-cultural makeup. This type of instrument can not only detect previously unrecognized but salient attributes of a local obesity problem, but can offer pathways for public health initiatives based on ORC nature and severity.

Conclusion

The new perspective of obesity as a chronic complex disease demands an integrated and structured approach to early detection of subjects at high risk. The AACE/ACE framework to diagnose obesity identifies greater numbers of subjects with ORC at lower levels of fat mass in Venezuela, translating to a higher preponderance of cardiometabolic risk, socio-economic burden, and public health challenges. Thus, structured programs and policies must be expeditiously formulated, transculturalized, and implemented to seize control over a massive obesity problem by preventing and

managing ORC.

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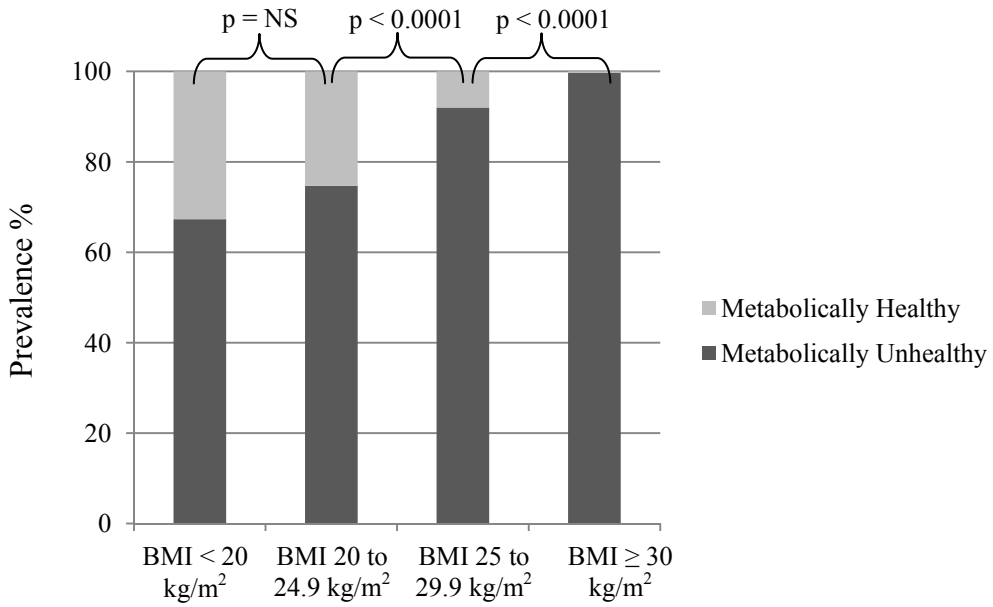

Figure 1: Proportion of subjects metabolically healthy and unhealthy according to body mass index (BMI). Subjects with cardiometabolic disease stage 0 (no metabolic risk factors) were defined as metabolically healthy. Abbreviations: NS – no significant.

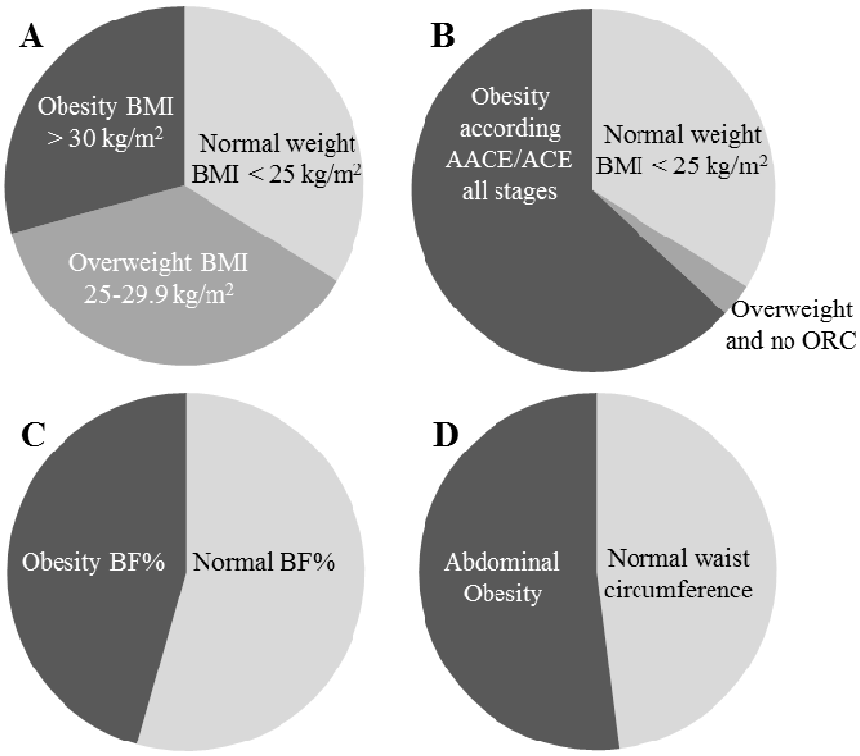

Figure 2: Variability in the capacity to detect obesity according to the definitions discussed. A) Obesity according to BMI cut-off. B) Obesity according to the AACE/ACE framework. All stages obesity include 0 – 2. C) Obesity according increased body fat percent (BF%) using bioimpedance. D) Abdominal obesity according increased waist circumference. Abbreviations: AACE: American Association of Clinical Endocrinologists. ACE: American College of Endocrinology. BF%: body fat percent. ORC: obesity related complications.

Table 1: Staging of Obesity-Related Complications Using the AACE/ACE Diagnostic Framework	
A) Prediabetes, metabolic syndrome and type 2 diabetes	
Stage 0 (none)	No risk factors related to insulin resistance (WC, BP, HDL-c, TG or FBG) (Equivalent to CMDS stage 0)[19]
Stage 1 (mild-moderate)	1 or 2 risk factors (WC, BP, HDL-c, or TG) (CMDS stage 1)
Stage 2 (severe)	Prediabetes, MS, or T2D (CMDS stages 2-4)
B) Hypertension	
Stage 0 (none)	BP < 130/85 mm/Hg (CMDS stage 0)
Stage 1 (mild-moderate)	BP ≥ 130/85 mm/Hg in absence of other risk factors (CMDS stage 1)
Stage 2 (severe complication)	BP target not met despite use of anti-hypertensive medication(s), BP ≥ 130/85 mm/Hg in high risk individual (CMDS 2 to 4)
c) High TG/Dyslipidemia	
Stage 0 (none)	TG < 150 mg/dl and HDL-c ≥ 40 mg/dl in male and ≥ 50 mg/dl in female (CMDS stage 0)
Stage 1 (mild-moderate)	TG 150 to 399 mg/dl and/or HDL-c < 40 mg/dl in male and < 50 mg/dl in female in absence of other risk factors (CMDS stage 1)
Stage 2 (severe)	TG ≥ 400 mg/dl in absence of other risk factors, TG ≥ 150 mg/dl and HDL-c < 40mg/dl in male and < 50 mg/dl in female in high risk individual (CMDS stage 2 to 4)
The Cardiometabolic Disease Stage System (CMDS)	
Stage 0	Metabolically healthy
Stage 1	One or two MS factors (other than IFG)
Stage 2	IFG or MS (three or more MS factors) but without IFG
Stage 3	MS with IFG
Stage 4	T2D or CVD

Abbreviations: BP: Blood pressure; CMDS: Cardiometabolic Disease Stage; CVD: Cardiovascular disease; FBG: Fasting blood glucose; HDL-c: High density lipoprotein cholesterol; IFG: Impaired fasting glucose; MS: Metabolic syndrome; T2D: Type 2 diabetes; TG: Triglycerides; WC: Waist circumference.

Table 2: Subject characteristics and prevalence of obesity and obesity-related complications (ORC) staging according AACE/ACE framework in five populations from Venezuela

	Men	Women	Total
Participants (n, %)	412 (31.2)	908 (68.8)	1320 (100.0)
Age (years)	45.8 ± 14.8	44.4 ± 14.1	44.8 ± 14.3
Weight (kilograms)*	80.1 ± 16.4	67.9 ± 14.4	71.7 ± 16.1
Height (meters)*	1.69 ± 0.07	1.56 ± 0.06	1.60 ± 0.09
BMI (kilograms/meters^2)	27.7 ± 5.1	27.6 ± 5.3	27.6 ± 5.2
Waist Circumference*	96.4 ± 13.2	89.8 ± 12.3	91.9 ± 13.0
Body fat %*	26.2 ± 8.7	33.6 ± 7.4	31.5 ± 8.5
Prevalence of obesity according to the AACE/ACE framework			
Normal weight	32.0 (27.5 - 36.5)	34.8 (31.7 – 37.9)	33.9 (31.4 - 36.5)
Overweight	2.4 (0.9 - 3.9)	3.2 (2.1 - 4.3)	3.0 (2.1 - 3.9)
Obesity stage 0	0.0 (0.0 - 0.0)	0.1 (-0.1 - 0.3)	0.1 (-0.07 - 0.27)
Obesity stage 1	23.1 (19.0 - 27.2)	28.2 (25.3 - 31.1)	26.6 (24.2 – 29.0)
Obesity stage 2†	42.5 (37.7 - 47.3)	33.7 (30.6 - 36.8)	36.4 (33.8 - 39.0)

Continues variables are mean ± SD. *Difference between genders $p < 0.001$.
Frequencies are % (95% CI). †Difference between genders $p= 0.03$
Body fat % was measured by bioimpedance.
Overweight: BMI ≥ 25 to 29.9 kg/m2 and no ORC (stage 0)
Obesity: BMI ≥ 30 kg/m2 and no ORC (stage 0)
Obesity stage 1: BMI ≥ 25 kg/m2 and presence of one or more mild-to-moderate ORC
Obesity stage 2: BMI ≥ 25 kg/m2 and presence of one or more severe ORC
Abbreviations: BMI - body mass index; ORC – obesity-related complications.

Table 3: Cardiometabolic Disease Stage (CMDS) and Cardiometabolic Risk Factors According to BMI

	BMI < 25 kg/m^2 n= 448	BMI 25 to 29.9 kg/m^2 n= 486	BMI ≥ 30 kg/m^2 n= 386
A- CMDS			
Stage 0*	26.1 (22.0 – 30.2)	8.0 (5.5 – 10.5)	0.3 (-0.2 – 0.8)
Stage 1*	52.9 (48.3 - 57.5)	47.1 (42.5 – 51.7)	39.1 (34.2 – 43.9)
Stage 2*	10.0 (7.2 - 12.8)	23.3 (19.4 – 27.2)	37.0 (32.1 – 41.8)
Stage 3*	3.3 (1.7 - 5.0)	13.8 (10.6 – 17.0)	13.7 (10.2 – 17.1)
Stage 4	7.6 (5.2 - 10.1)	7.8 (5.3 – 10.3)	9.8 (6.8 – 12.7)
B- Cardiometabolic risk factors			
Systolic blood pressure (mmHg)†	114.3 ± 16.0 [a]	122.7 ± 18.8 [b]	127.2 ± 19.2 [c]
Diastolic blood pressure (mmHg)†	72.8 ± 10.3 [a]	78.5 ± 13.2 [b]	81.5 ± 13.0 [c]
Total cholesterol (mg/dL) †	196.2 ± 45.2 [a]	212.6 ± 46.5 [b]	211.6 ± 48.2 [b]
LDL-c (mg/dL)†	123.5 ± 41.0 [a]	135.5 ± 43.8 [b]	134.9 ± 45.4 [b]
HDL-c (mg/dL)†	48.2 ± 11.8 [a]	45.6 ± 10.6 [b]	43.8 ± 10.3 [c]
Triglycerides (mg/dL) †	124.8 ± 79.3 [a]	160.9 ± 117.6 [b]	169.1 ± 113.9 [b]
Blood glucose (mg/dL)	82.2 ± 17.0 [a]	87.0 ± 21.2 [a]	87.0 ± 20.0 [a]

Frequencies are % (95% CI).
*Difference between BMI categories using Chi-square $p < 0.0001$
Stage 0: metabolically healthy
Stage 1: one or two metabolic syndrome risk factors (other than impaired fasting glucose ([IFG])
Stage 2: IFG or metabolic syndrome (without IFG)
Stage 3: IFG plus metabolic syndrome
Stage 4: type 2 diabetes mellitus/cardiovascular disease
Continues variables are mean and SD. Blood glucose is median and Interquartile Range (IR).
Differences of means of each cardiometabolic risk factor according BMI categories were evaluated with one way ANOVA and Tukey post-hoc, and medians of blood glucose with Mann-Whitney U test, † $p < 0.05$. Values of the same row with different letters represent differences ($p < 0.05$) between BMI categories. Abbreviation: BMI- body mass index; HDL-c – high density lipoprotein cholesterol; LDL-c – low density lipoprotein cholesterol.

Table 4: Prevalence of obesity according to others definitions.

	Men	Women	Total
A) According by WHO definition			
Obesity: BMI ≥ 30 kg/m^2	27.9 (23.4 - 32.4)	29.8 (25.2 - 34.4)	29.3 (24.7 - 33.7)
Overweight: BMI ≥ 25 to 29.9 kg/m^2	40.0 (35.6 - 44.4)	35.4 (31.2 - 39.7)	36.8 (34.3 - 42.9)
Underweight: BMI < 18.5 kg/m^2	1.0 (0.04 – 1.96)	1.2 (0.49 – 1.91)	1.1 (0.54 – 1.66)
B) According by waist circumference: ≥ 94 cm in men and ≥ 90 cm in women			
Abdominal Obesity*	57.8 (53.0- 62.6)	49.4 (46.2 - 52.7)	52.0 (49.3 - 54.7)
C) According by body fat (BF)%: > 25% in men and > 35% in women			
BF%-Obesity†	49.7 (44.9 - 54.5)	43.9 (40.7 - 47.1)	45.6 (42.9 - 48.3)

Data are % (95% CI). *Difference between genders: p = 0.005
†529 of participants complete this data.
Abbreviations: BMI- Body mass index; BF%- Body fat percent; WHO- World Health Organization.

Table 5: Prevalence of obesity according to WHO categories by age and gender

	Prevalence		Logistic regression	
Age groups n (% women)	Men (412)	Women (908)	OR	Significance
20 to 29; 221(70.1)	9.6 (6.7 – 12.4)	10.0 (8.1 – 11.9)	1.0	
30 to 39; 286 (71.5)	21.7 (17.4 – 25.3)	21.4 (18.7 – 24.1)	1.9 (1.3 - 3.0)	p= 0.002
40 to 49; 323 (67.8)	34.8 (30.2 – 39.4)	26.6 (23.7 – 29.4)	2.5 (1.7 - 3.8)	p< 0.001
50 to 59; 256 (73.0)	18.3 (14.4 – 22.0)	21.8 (19.1 – 24.4)	2.2 (1.4 - 3.4)	p< 0.001
60 to 69; 179 (61.5)	13.9 (10.5 – 17.2)	16.6 (14.1 – 19.0)	2.5 (1.5 - 3.9)	p< 0.001
70 and + ; 55 (58.2)	1.7 (0.4 – 2.9)	3.7 (2.4 – 4.9)	1.3 (0.6 - 2.7)	p= 0.427

Abbreviations: WHO: World Health Organization. CI: confidence intervals. OR: odds ratio.
Prevalence are percent and 95% CI

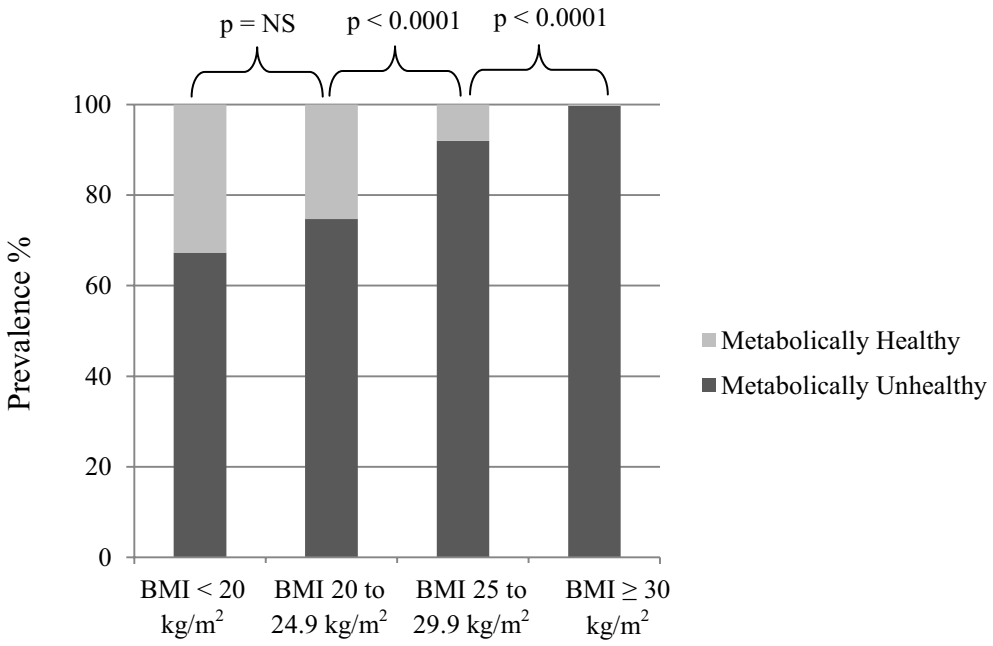

Figure 1: Proportion of subjects metabolically healthy and unhealthy according to body mass index (BMI). Subjects with cardiometabolic disease stage 0 (no metabolic risk factors) were defined as metabolically healthy. Abbreviations: NS – no significant.

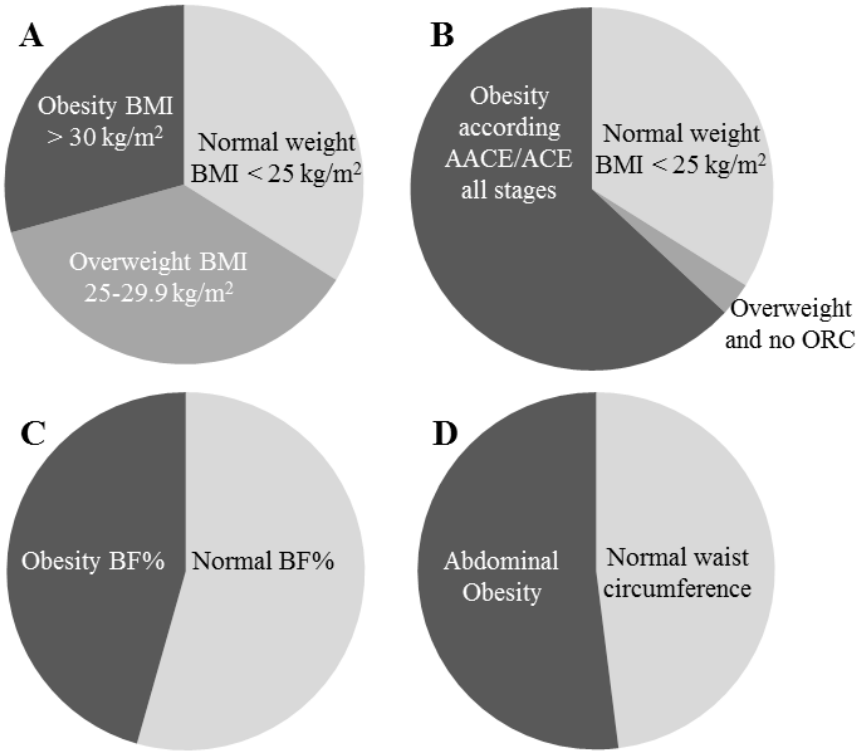

Figure 2: Variability in the capacity to detect obesity according to the definitions discussed. A) Obesity according to BMI cut-off. B) Obesity according to the AACE/ACE framework. All stages obesity include 0 – 2. C) Obesity according increased body fat percent (BF%) using bioimpedance. D) Abdominal obesity according increased waist circumference. Abbreviations: AACE: American Association of Clinical Endocrinologists. ACE: American College of Endocrinology. BF%: body fat percent. ORC: obesity related complications.

Table 1: Staging of Obesity-Related Complications Using the AACE/ACE Diagnostic Framework	
A) Prediabetes, metabolic syndrome and type 2 diabetes	
Stage 0 (none)	No risk factors related to insulin resistance (WC, BP, HDL-c, TG or FBG) (Equivalent to CMDS stage 0)[19]
Stage 1 (mild-moderate)	1 or 2 risk factors (WC, BP, HDL-c, or TG) (CMDS stage 1)
Stage 2 (severe)	Prediabetes, MS, or T2D (CMDS stages 2-4)
B) Hypertension	
Stage 0 (none)	BP < 130/85 mm/Hg (CMDS stage 0)
Stage 1 (mild-moderate)	BP ≥ 130/85 mm/Hg in absence of other risk factors (CMDS stage 1)
Stage 2 (severe complication)	BP target not met despite use of anti-hypertensive medication(s), BP ≥ 130/85 mm/Hg in high risk individual (CMDS 2 to 4)
c) High TG/Dyslipidemia	
Stage 0 (none)	TG < 150 mg/dl and HDL-c ≥ 40 mg/dl in male and ≥ 50 mg/dl in female (CMDS stage 0)
Stage 1 (mild-moderate)	TG 150 to 399 mg/dl and/or HDL-c < 40 mg/dl in male and < 50 mg/dl in female in absence of other risk factors (CMDS stage 1)
Stage 2 (severe)	TG ≥ 400 mg/dl in absence of other risk factors, TG ≥ 150 mg/dl and HDL-c < 40mg/dl in male and < 50 mg/dl in female in high risk individual (CMDS stage 2 to 4)
The Cardiometabolic Disease Stage System (CMDS)	
Stage 0	Metabolically healthy
Stage 1	One or two MS factors (other than IFG)
Stage 2	IFG or MS (three or more MS factors) but without IFG
Stage 3	MS with IFG
Stage 4	T2D or CVD

Abbreviations: BP: Blood pressure; CMDS: Cardiometabolic Disease Stage; CVD: Cardiovascular disease; FBG: Fasting blood glucose; HDL-c: High density lipoprotein cholesterol; IFG: Impaired fasting glucose; MS: Metabolic syndrome; T2D: Type 2 diabetes; TG: Triglycerides; WC: Waist circumference.

Table 2: Subject characteristics and prevalence of obesity and obesity-related complications (ORC) staging according AACE/ACE framework in five populations from Venezuela

	Men	Women	Total
Participants (n, %)	412 (31.2)	908 (68.8)	1320 (100.0)
Age (years)	45.8 ± 14.8	44.4 ± 14.1	44.8 ± 14.3
Weight (kilograms)*	80.1 ± 16.4	67.9 ± 14.4	71.7 ± 16.1
Height (meters)*	1.69 ± 0.07	1.56 ± 0.06	1.60 ± 0.09
BMI (kilograms/meters^2)	27.7 ± 5.1	27.6 ± 5.3	27.6 ± 5.2
Waist Circumference*	96.4 ± 13.2	89.8 ± 12.3	91.9 ± 13.0
Body fat %*	26.2 ± 8.7	33.6 ± 7.4	31.5 ± 8.5
Prevalence of obesity according to the AACE/ACE framework			
Normal weight	32.0 (27.5 - 36.5)	34.8 (31.7 – 37.9)	33.9 (31.4 - 36.5)
Overweight	2.4 (0.9 - 3.9)	3.2 (2.1 - 4.3)	3.0 (2.1 - 3.9)
Obesity stage 0	0.0 (0.0 - 0.0)	0.1 (-0.1 - 0.3)	0.1 (-0.07 - 0.27)
Obesity stage 1	23.1 (19.0 - 27.2)	28.2 (25.3 - 31.1)	26.6 (24.2 – 29.0)
Obesity stage 2†	42.5 (37.7 - 47.3)	33.7 (30.6 - 36.8)	36.4 (33.8 - 39.0)

Continues variables are mean ± SD. *Difference between genders $p < 0.001$.
Frequencies are % (95% CI). †Difference between genders $p= 0.03$
Body fat % was measured by bioimpedance.
Overweight: BMI ≥ 25 to 29.9 kg/m2 and no ORC (stage 0)
Obesity: BMI ≥ 30 kg/m2 and no ORC (stage 0)
Obesity stage 1: BMI ≥ 25 kg/m2 and presence of one or more mild-to-moderate ORC
Obesity stage 2: BMI ≥ 25 kg/m2 and presence of one or more severe ORC
Abbreviations: BMI - body mass index; ORC – obesity-related complications.

Table 3: Cardiometabolic Disease Stage (CMDS) and Cardiometabolic Risk Factors According to BMI

	BMI < 25 kg/m^2 n= 448	BMI 25 to 29.9 kg/m^2 n= 486	BMI ≥ 30 kg/m^2 n= 386
A- CMDS			
Stage 0*	26.1 (22.0 – 30.2)	8.0 (5.5 – 10.5)	0.3 (-0.2 – 0.8)
Stage 1*	52.9 (48.3 - 57.5)	47.1 (42.5 – 51.7)	39.1 (34.2 – 43.9)
Stage 2*	10.0 (7.2 - 12.8)	23.3 (19.4 – 27.2)	37.0 (32.1 – 41.8)
Stage 3*	3.3 (1.7 - 5.0)	13.8 (10.6 – 17.0)	13.7 (10.2 – 17.1)
Stage 4	7.6 (5.2 - 10.1)	7.8 (5.3 – 10.3)	9.8 (6.8 – 12.7)
B- Cardiometabolic risk factors			
Systolic blood pressure (mmHg)†	114.3 ± 16.0 [a]	122.7 ± 18.8 [b]	127.2 ± 19.2 [c]
Diastolic blood pressure (mmHg)†	72.8 ± 10.3 [a]	78.5 ± 13.2 [b]	81.5 ± 13.0 [c]
Total cholesterol (mg/dL) †	196.2 ± 45.2 [a]	212.6 ± 46.5 [b]	211.6 ± 48.2 [b]
LDL-c (mg/dL)†	123.5 ± 41.0 [a]	135.5 ± 43.8 [b]	134.9 ± 45.4 [b]
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Blood glucose (mg/dL)	82.2 ± 17.0 [a]	87.0 ± 21.2 [a]	87.0 ± 20.0 [a]

Frequencies are % (95% CI).
*Difference between BMI categories using Chi-square $p < 0.0001$
Stage 0: metabolically healthy
Stage 1: one or two metabolic syndrome risk factors (other than impaired fasting glucose ([IFG])
Stage 2: IFG or metabolic syndrome (without IFG)
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Differences of means of each cardiometabolic risk factor according BMI categories were evaluated with one way ANOVA and Tukey post-hoc, and medians of blood glucose with Mann-Whitney U test, † $p < 0.05$. Values of the same row with different letters represent differences ($p < 0.05$) between BMI categories. Abbreviation: BMI- body mass index; HDL-c – high density lipoprotein cholesterol; LDL-c – low density lipoprotein cholesterol.

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Underweight: BMI < 18.5 kg/m^2	1.0 (0.04 – 1.96)	1.2 (0.49 – 1.91)	1.1 (0.54 – 1.66)
B) According by waist circumference: ≥ 94 cm in men and ≥ 90 cm in women			
Abdominal Obesity*	57.8 (53.0- 62.6)	49.4 (46.2 - 52.7)	52.0 (49.3 - 54.7)
C) According by body fat (BF)%: > 25% in men and > 35% in women			
BF%-Obesity†	49.7 (44.9 - 54.5)	43.9 (40.7 - 47.1)	45.6 (42.9 - 48.3)

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†529 of participants complete this data.

Abbreviations: BMI- Body mass index; BF%- Body fat percent; WHO- World Health Organization.

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30 to 39; 286 (71.5)	21.7 (17.4 – 25.3)	21.4 (18.7 – 24.1)	1.9 (1.3 - 3.0)	p= 0.002
40 to 49; 323 (67.8)	34.8 (30.2 – 39.4)	26.6 (23.7 – 29.4)	2.5 (1.7 - 3.8)	p< 0.001
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70 and + ; 55 (58.2)	1.7 (0.4 – 2.9)	3.7 (2.4 – 4.9)	1.3 (0.6 - 2.7)	p= 0.427

Abbreviations: WHO: World Health Organization. CI: confidence intervals. OR: odds ratio. Prevalence are percent and 95% CI