RESEARCH ARTICLE

REVISED Biochemical and clinical characterization of metabolic phenotypes: a cross-sectional study from Maracaibo city, Venezuela [version 3; peer review: 2 approved, 1 approved with reservations]

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Abstract

Background: In 1980, Reuben Andresen observed that in certain individuals, obesity did not increase mortality, introducing an atypical phenotype called "healthy obese". Other studies reported that 10-15 % of lean individuals presented insulin resistance, hyperglycemia and dyslipidemia. The objective of this study was to evaluate biochemical and clinical characteristics of metabolic phenotypes in Maracaibo city.
Methods: A descriptive, cross-sectional sub-analysis of The Maracaibo City Metabolic Syndrome Prevalence Study, with a randomized multistage sampling was performed including 1226 non diabetic individuals from both sexes. For phenotype definition, the subjects were first classified according to their BMI into Normal-Weight, Overweight and Obese; then divided in metabolically healthy and unhealthy using a two-step analysis cluster being predictive variables: HOMA2-IR, HOMA2-βcell, triglycerides. To evaluate the relationship with coronary risk, a multiple logistic regression model was performed.
Results: In the studied population, 43.9% (n=538) were healthy normal weight, 5.2% (n=64) unhealthy normal weight, 17.4% (n=217) healthy obese and 33.5% (n=411) unhealthy obese subjects. Atypical

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phenotypes, Metabolically Unhealthy Normal-Weight (MUNW) was more frequent in males (56.3%), whereas Metabolically Unhealthy Obese (MUO) was more frequent in females (51.3%). This phenotypes had a higher coronary event risk, especially for obese individuals (MHO: OR=1.85 CI95%: 1.11-3.09; p=0.02 and MUO: OR=2.09 CI95%: 1.34-3.28; p<0.01).

Conclusion: Individuals with atypical metabolic phenotypes are common in Maracaibo city. Related factors may include insulin resistance, basal glucose, and triglycerides levels. Lastly, obese subjects show a higher coronary event risk even those with normal metabolic status.

Keywords
Metabolic phenotypes, two-step cluster, metabolically unhealthy lean, metabolically healthy obese, coronary risk

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Any reports and responses or comments on the article can be found at the end of the article.

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REVISED **Amendments from Version 2**

We want to appreciate the comments of the reviewer, regarding the last revision:

1. We also consider that the definition of "metabolically healthy obesity" is arbitrary, therefore our line of research tried to identify the main metabolic variables that could predict the state of "health / disease" through a cluster analysis that was not influenced by variables fixed a priori. (J Diabetes Res. 2015; 2015: 750265). Although this phenotype is controversial, it has been described in numerous studies (J Clin Invest. 2019; 129 (10): 3978–3989 / Endocrine Reviews 2020; 41 (3): 405–420) and as we argue based on our findings, the erroneous perception of being a "healthy" phenotype does not indicate that it is not a biological phenotype (probably of early presentation within the natural history of cardiometabolic disease) (https://doi.org/10.1530/EJE-15-0449).

2. We agree that the body mass index and waist circumference are anthropometric measures of low diagnostic precision, however they are recommended by the different international guidelines as an initial step in the approach to these individuals, especially in low-resource contexts, where the availability of imaging studies that quantify the degree of visceral adiposity are low due to high cost (https://doi.org/10.1530/EJE-19-0893. This represents a limitation of our study (which has been added.

3. The reviewer states that our study is: "a metabolically based categorization of the BMI". But to date the definition of metabolic phenotypes is based on this, with criteria set by groups of experts. A possible future alternative is to correlate the biochemical and clinical behavior of these phenotypes with imaging studies that provide more specific information about abdominal fat content.

Any further responses from the reviewers can be found at the end of the article

Introduction

Obesity is considered an entity with major morbi-mortality in the world since the end of the 20th century[1]. Multiples studies have shown its role as an independent risk factor for various cardiometabolic disorders such as hypertension (HTN), dyslipidemias, Type 2 Diabetes Mellitus (T2DM) and cardiovascular disease (CVD)[2]. For this reason, the actual clinical practice catalogues the typical obese patient as an "unhealthy" patient or a patient with comorbidities.

In spite of this, in 1980, Reuben Andresen discovered that in certain groups of individuals the obesity was not a mortality increasing factor, introducing the subtype "Healthy Obese"[3]. Around 20 years later, Ferranini *et al.* observed that a group of certain obese nondiabetic non-hypertensive subjects presented low insulin resistance (IR) prevalence, suggesting that this subtype must have a different risk of having T2DM and CVD from the IR obese; also suggesting a different management for them[4].

Furthermore, in 1975, Bernstein *et al.* observed that 11 normal-weight men with type IV or V dyslipidemia presented higher serum glucose levels; and also carried bigger sized adipocytes with respect to their healthy counterparts[5]. Years later, Ruderman *et al*. introduced the "Metabolically Unhealthy Normal-Weight" phenotype attributed to lean individuals with metabolic alterations associated to obesity[6].

The importance of these atypical metabolic phenotypes lies in the fact that their diagnosis may be challenging for clinicians delaying their detection. Because of this, in recent years, multiple studies have been dedicated to the research of accurate clinical, biochemical, and genetic elements capable to detect these atypical metabolic states, and their evolution. Likewise, it has been discussed whether the use of certain anthropometric parameters is enough to classify the subjects as healthy or sick from a cardiometabolic perspective.

In this sense, these phenotypes determinants and frequencies have not been deeply researched in Latin-American populations[7]. Despite the wide heterogeneity observed in our region influenced for genetic and environmental factors as well as the similar prevalence of cardiometabolic diseases in Maracaibo city and other localities from the continent. The objective of this study is to characterize, from a clinical-biological point of view, the metabolic phenotypes in the population from Maracaibo city, Venezuela.

Materials and methods

Population selection

The Maracaibo City Metabolic Syndrome Prevalence Study (MMSPS) is a cross-sectional study whose purpose is to detect metabolic syndrome and cardiovascular disease risk factors in the adult population from Maracaibo, the second largest city of Venezuela, with approximately 2,500,000 inhabitants, during the period May 2007 – December 2009. The original study included a total of 2230 individuals of both genders, aged between 18–85 years old, and the study protocol was previously reported[8]. This sub-analysis excluded those individuals with no measurements of serum insulin levels. Patients with past history of diabetes were also excluded because their disease control, evolution and pharmacological treatments would affect the variables in the study.

In order to avoid classifying the subjects according to *a priori* pre-established definitions, a cluster analysis was carried out that allowed selecting the main variables in the definition of healthy-sick subjects by data mining technique. In this way, these subjects were categorized into six groups, first according to their Body Mass Index (BMI) (normal-weight, overweight and obese) and second, to their healthy/unhealthy definition. This categorization was made using the protocol from two-step cluster analysis published previously[9]. The metabolic variables were chosen as possible metabolic predictors based on their physiological function and biological plausibility. These variables were: mean arterial pressure (MAP), triglycerides (TAG), total cholesterol, HDL-C, HOMA2-IR, HOMA2-βcell, HOMA2-S, fasting blood glucose, non-HDL-C cholesterol, TAG/HDL-C ratio, and high-sensitivity C-Reactive Protein (hs-CRP) levels; waist circumference (WC) was excluded and was assessed as a dependent variable.

The most appropriate predictive variables selected according predictive strength for each group were: (a) HOMA2-IR and HOMA2-βcell for normal-weight women; (b) HOMA2-IR, HOMA2-βcell and TAG for normal-weight men; (c) HOMA2-IR and HOMA2-βcell for overweight women; (d) HOMA2-IR, HOMA2-βcell, and TAG for overweight men; and (e) HOMA2-IR for male and female obese patients. The two-step cluster analysis was conducted with SPSS, the program analyzed the subclusters with the characteristics of each BMI category and categorized the subjects into 6 phenotypes: healthy normal-weight (HNW), metabolically unhealthy normal-weight (MUNW), healthy and metabolically disturbed overweight, metabolically unhealthy obese (MUO), and metabolically healthy obese (MHO). Overweight subjects were excluded from this secondary analysis since they represent a non-conventional group outside the metabolic phenotypes and require separate analysis. The final sample included 1226 subjects (Figure 1).

Clinical evaluation

Data was collected through completion of a full clinical record carried out by trained personnel, which included interrogation regarding ethnic origin and socioeconomic status by the Graffar scale according to Méndez-Castellano[10]. The assessment of blood pressure was done by applying the auscultatory technique, and HTN classification was made using the criteria proposed in the VII Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure[11].

For Anthropometric Analysis, an electrical bioelectric scale was used to obtain weight (Tanita, TBF-310 GS Body Composition Analyzer, Tokyo – Japan). Height was measured using a calibrated metric measurement tape, with the subject standing up barefoot. BMI formula (weight/height^2) was applied, expressing the results as kg/m^2. Obesity was classified applying the WHO criteria[12] based on the BMI value. Finally, WC was measured

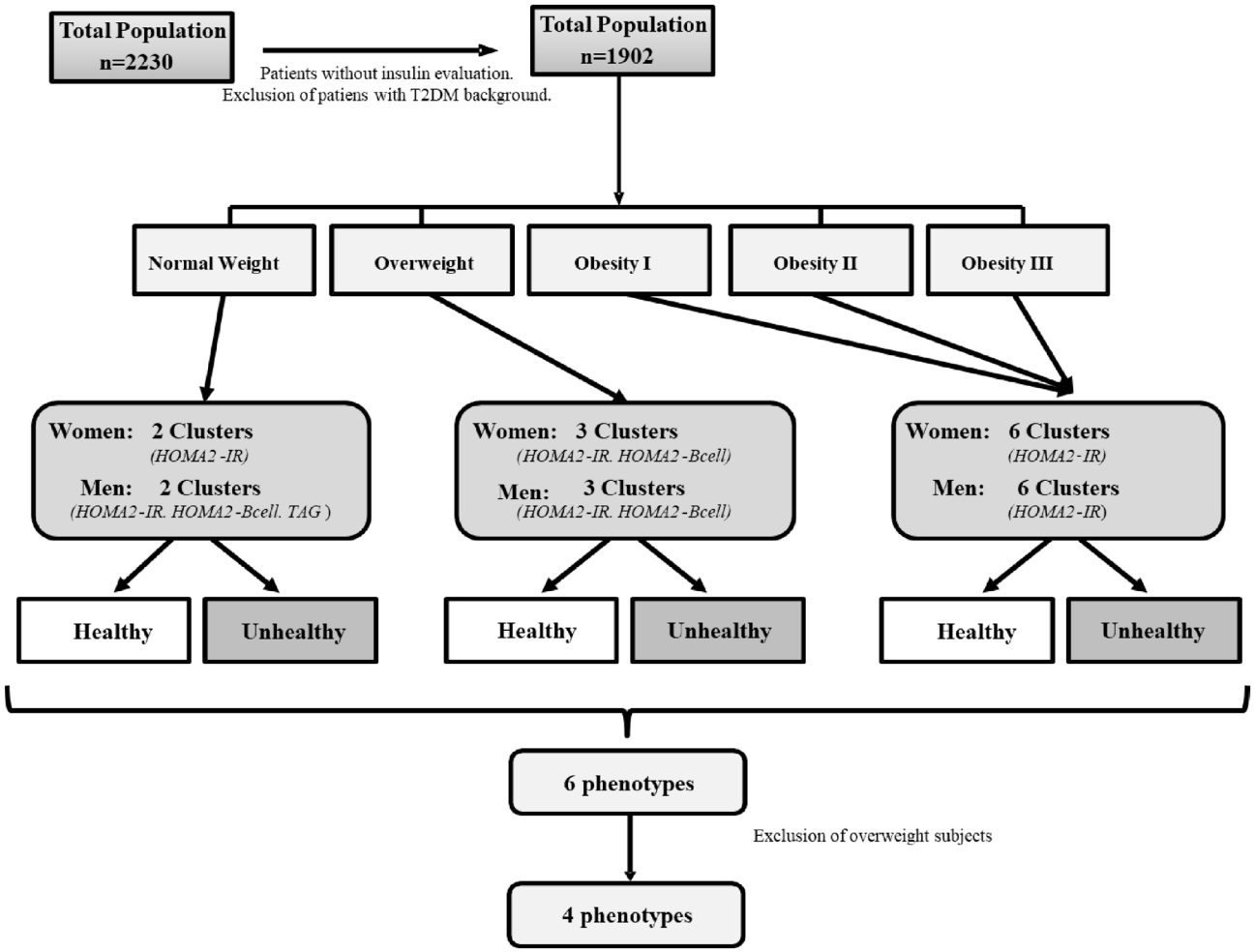

Figure 1. Patient selection diagram. Maracaibo city, Venezuela. During sample selection, subjects with no measurements of serum insulin levels and patients with past history of diabetes were excluded. These subjects were categorized into six groups, first according to their BMI and second to their healthy/unhealthy definition, using two-step cluster analysis.

using calibrated measuring tape in accordance to the anatomical landmarks proposed by the USA National Institutes of Health protocol[13].

Physical activity. Physical activity (PA) was assessed with the International Physical Activity Questionnaire (IPAQ). For statistical analysis, PA was evaluated in 4 domains: occupational, household, transport, and leisure. In each of these domains, subjects were categorized as follows: (a) inactive, MET/week = 0, or (b) active, MET/week > 0.

Biochemical analyses

Fasting levels of glucose, cholesterol, TAG, HDL-C, and hs-CRP were assessed in our clinical laboratory using an automatized computer analyzer (Human Gesellschaft fur Biochemica und Diagnostica mbH). LDL-C and VLDL-C levels were calculated applying the Friedewald formulas[14]. When TAG were over 400 mg/dL measurement was done using lipoprotein electrophoresis and optical densitometry (BioRad GS-800 densitometer, USA). Lipoprotein (a) [Lp(a)] was estimated through the latex turbidimetric method, Human Gesellschaft für Biochemica and Diagnostica, Germany. Likewise, serum hs-CRP levels were quantified employing immunoturbidimetric essays (Human Gesellschaft für Biochemica and Diagnostica MBH). Insulin was determined using an ultrasensitive ELISA method (DRG Instruments GmbH, Germany, International DRG Division, Inc.). For the evaluation of insulin resistance (IR), 2 was the cut-off to define it 15, the HOMA2-IR model proposed by Levy *et al.* was utilized[16] determined through the HOMA-Calculator v2.2.2 program. Visceral Adiposity Index (VAI) calculation was performed with the gender-specific equations proposed by Amato *et al.*[17]. The Metabolic Syndrome (MS) diagnosis was done using the Harmonizing-2009 consensus criteria[18].

Calibration of the Framingham-Wilson equation and coronary risk categorization for the population of Maracaibo city

For proper equation calibration, the constants in the formula regarding major cumulative coronary events (lethal and non-lethal, symptomatic and no symptomatic myocardial infarction, angina) were substituted with the local statistics obtained from the Vital Statistics Yearbook of the State of Zulia from 2008, where the morbidity and mortality for cardiovascular diseases is registered, the calibration process has been detailed previously[19]. The coronary risk was classified in 2 categories: <5% in 10 years, and ≥5% in 10 years.

Statistical analysis

Normal distribution of continuous variables was assessed using Geary's test; for normally distributed variables, the results were expressed as arithmetic mean ± SD (standard deviation). Variables without normal distribution were logarithmically transformed, and normal distribution subsequently corroborated. When normalization could not be achieved, these variables were expressed as medians (25^{th} percentile–75^{th} percentile). Student's –test/One-way ANOVA or Mann-Whitney/Kruskal Wallis's tests were applied to evaluate differences between means or medians, respectively. Qualitative variables were expressed as absolute and relative frequencies, assessed through the χ^2 test and the Z test for Proportions.

A logistic regression model was constructed with coronary risk as dependent variable and independent variables: gender, age groups, ethnicity, socioeconomic status, smoking habit, physical activity in leisure time, elevated TAG, and metabolic phenotypes. Database construction and statistical analysis were done using the Statistical Package for the Social Sciences (SPSS) v22 for Windows (IBM Inc., Chicago, IL), results were considered statistically significant when $p<0.05$.

Results

Population general characteristics

A total of 1226 individuals were studied, 55.1% (n=676) corresponded to females and 44.9% (n=550) to males. The mean age (years) of the general population was 37.94±14.99. Subjects distribution according to their metabolic phenotype is shown in Figure 2 where the 5.2% (n=64) of the individuals were classified as MUNW, and 17.4% (n=213) as MHO, representing 34.13% from the total of obese subjects, while sociodemographic and metabolic characteristics from the studied simple are shown in Table 1.

Metabolic phenotypes and sociodemographic characteristics

In the evaluation of the epidemiologic behavior of the metabolic phenotypes according to sex, we found that HNW and MUO individuals were predominately females (62.5%, n=336; 51.3%, n=211 respectively), while the atypical phenotypes were predominately males (MUNW: 56.3%, n=36; MHO: 52.6%, n=112. χ^2=22.53, p<0.001). Likewise, a statistically significant association was found between age groups and metabolic phenotypes (χ^2= 211.91, p<0.001), observing a predominance in the < 30 years age group in the normal-weight phenotype (HNW: 56.1%, n=302; MUNW: 57.8%, n=37), whereas the 30–49 age group was predominately obese phenotypes (MHO: 47.9%, n=102;

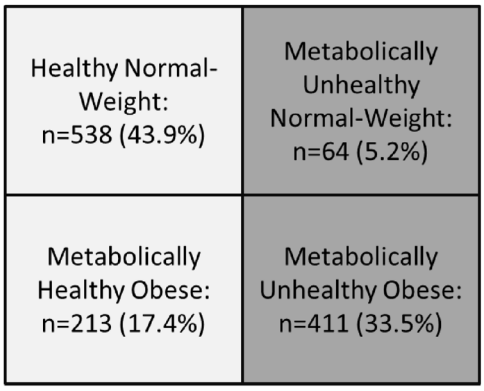

Figure 2. Distribution of individuals according to metabolic phenotypes. Maracaibo city, Venezuela. For this sub-analysis overweight subjects were excluded, evaluating only the typical obesity phenotypes with 4 groups.

Table 1. General Characteristics of the studied sample. Maracaibo city, Venezuela.

	Female		Male		Total	
	n	%	n	%	n	%
Age Group (years)						
<30	235	34.8	228	41.5	463	37.8
30–49	253	37.4	220	40.0	473	38.6
≥50	188	27.8	102	18.5	290	23.7
Ethnic Groups						
Mixed	512	75.7	427	77.6	939	76.6
White Hispanic	111	16.4	80	14.5	191	15.6
Afrodescendant	15	2.2	21	3.8	36	2.9
Native-American	30	4.4	21	3.8	51	4.2
Other	8	1.2	1	0.2	9	0.7
Socioeconomic Status						
Class I	15	2.2	9	1.6	24	2.0
Class II	116	17.2	113	20.5	229	18.7
Class III	253	37.4	237	43.1	490	40.0
Class IV	251	37.1	172	31.3	423	34.5
Class V	41	6.1	19	3.5	60	4.9
Smoking Habit						
No Smoker	523	77.5	351	64.3	874	71.6
Smoker	76	11.3	105	19.2	181	14.8
Past Smoker	76	11.3	90	16.5	166	13.6
Hypertension‡	126	18.6	144	26.2	270	22.0
Elevated Triglycerides	139	20.6	170	30.9	309	25.2
Low HDL-C	429	63.5	270	49.1	699	57.0
Metabolic Syndrome*	250	37.0	233	42.4	483	39.4
Insulin Resistance†	317	46.9	257	46.7	574	46.8
Total	**676**	**100.0**	**550**	**100.0**	**1226**	**100.0**

‡ Past history and Diagnosed in the Study

* Metabolic Syndrome Diagnosis according to 2009 Harmonizing Consensu

† HOMA2-IR ≥2

MUO: 50.1%, n=106). There was no statistically significant association between metabolic phenotypes, ethnic groups (χ^2= 20.96, p=0.05) and socioeconomic status (χ^2= 14.56, p=0.27) (Table 2).

Metabolic phenotypes and psychobiologic habits

Initially, in relation to the smoking habit, the non-smokers were the most frequent group (χ^2=30.91; p<0.001), despite the fact MUNW phenotype consisted of the highest percentage of smoking individuals (18.8%, n=12), whereas MUO subjects consisted of the highest proportion of past smoking subjects (20.2%, n=83). On the other side, in the evaluation of the metabolic phenotypes according to PA there was a statistically significant association in the transport-related physical activity (χ^2=26.93; p<0.001) and leisure activities (χ^2=19.75; p<0.001) (Table 3).

Phenotypes and endocrine-metabolic alterations

Distribution of subjects according to phenotypes and endocrine-metabolic alterations are shown in Table 4. A high percentage of MUNW and MUO individuals with insulin resistance was found in contrast to healthy subjects (79.7%, n=51 and 97.1%, n=399, respectively). On the other side, a higher percentage of MUNW with high TAG was found (34.4% n=22 vs 9.5% n=51 HNW; p<0.05) and also a higher prevalence of MS (29.7% n=19 vs 12.3% n=66; p<0.05 HNW); similar findings were observed in the obese phenotypes, where a minor prevalence of these alterations were found in the MHO subjects (high TAG levels: 28.8% n=60 vs 42.8% n=176, p<0.05; MS: 53.1% n=113 vs 69.3% n=285, p<0.05). Finally, a significant association was found between the metabolic phenotypes with low HDL-C (χ^2=44.08; p<0.0001) and HTN (χ^2= 182.22, p<0.0001).

Metabolic phenotypes and biologic-anthropometric variables

Biochemical and clinical characteristics according to metabolic phenotypes are shown in Table 5. An increasing tendency of their variable levels was observed, except on HOMA2-IR, HOMA2-βcell, HOMA2-S, insulin and glucose levels whose values were higher in sick subjects; while individuals with obesity had lower levels of HDL-C.

Metabolic phenotypes and coronary risk classification

An association between metabolically unhealthy phenotypes and a higher risk of a coronary event was found in univariate analysis. However, results were statistically significant only for obese individuals when multivariate adjustment was applied (MHO: OR=1.85 CI95%: 1.11-3.09; p=0.02 and MUO: OR=2.09 CI95%: 1.34-3.28; p<0.01) (Table 6).

Discussion

Obesity is a prioritized area for the world health systems because of its increasing prevalence, incidence, and associated costs in the last decade[20]. This disease has been defined classically as "excessive presence of adipose tissue that is injurious for health" and given its association to other chronic-degenerative diseases[3,21] has been stereotyped as "more adiposity, more risk". All the classic methods employed for obesity diagnosis, even central and global, are indirect measurements. For different populations they do not allow to determine the adipose tissue functioning from

Table 2. Sociodemographic characteristics according to metabolic phenotypes. Maracaibo city, Venezuela.

	(HNW) A		(MUNW) B		(MHO) C		(MUO) D			A vs. B	A vs. C	A vs. D	B vs. C	B vs. D	C vs. D
	n	%	n	%	n	%	n	%	$\chi 2$ (*p*)*	*p***	*p***	*p***	*p***	*p***	*p***
Gender									22.53 (<0.001)						
Female	336	62.5	28	43.8	101	47.4	211	51.3		<0.05	<0.05	<0.05	NS	NS	NS
Male	202	37.5	36	56.3	112	52.6	200	48.7		<0.05	<0.05	<0.05	NS	NS	NS
Age Group (years)									176.63 (<0.001)						
<30	302	56.1	37	57.8	46	21.6	78	19.0		NS	<0.05	<0.05	<0.05	<0.05	NS
30–49	153	28.4	12	18.8	102	47.9	206	50.1		NS	<0.05	<0.05	<0.05	<0.05	NS
≥50	83	15.5	15	23.4	65	30.5	127	30.9		NS	<0.05	<0.05	NS	NS	NS
Ethnic Group									20.96 (0.05)						
Mixed	412	76.6	50	78.1	169	79.3	308	74.9		NS	NS	NS	NS	NS	NS
White Hispanic	74	13.8	6	9.4	31	14.6	80	19.5		NS	NS	NS	NS	NS	NS
Afrodescendant	16	3.0	3	4.7	6	2.8	11	2.7		NS	NS	NS	NS	NS	NS
Native-American	32	5.9	5	7.8	6	2.8	8	1.9		NS	NS	<0.05	NS	<0.05	NS
Others	4	0.7	0	0.0	1	0.5	4	1.0		NS	NS	NS	NS	NS	NS
Socioeconomic Status									14.56 (0.27)						
Class I	12	2.2	0	0.0	2	0.9	10	2.4		NS	NS	NS	NS	NS	NS
Class II	96	17.8	15	23.4	35	16.4	83	20.2		NS	NS	NS	NS	NS	NS
Class III	213	39.6	21	32.8	102	47.9	154	37.5		NS	NS	NS	NS	NS	NS
Class IV	187	34.8	25	39.1	62	29.1	149	36.3		NS	NS	NS	NS	NS	NS
Class V	30	5.6	3	4.7	12	5.6	15	3.6		NS	NS	NS	NS	NS	NS
Total	**538**	**100**	**64**	**100**	**213**	**100**	**411**	**100**							

HNW (Healthy Normal Weight); MUNW (Metabolically Unhealthy Normal Weight); MHO (Metabolically Healthy Obese); MUO (Metabolically Unhealthy Obese).

* Chi-Square Test.

** Z-test of proportions.

individuals, even though they have high sensitivity, specificity, and predictive values. Based on this, multiple epidemiologic studies have detected a considerable percentage of individuals who did not enter in the classic "HNW" and "MUO" phenotypes, showing the existence of atypical metabolic phenotypes called "MUNW" and "MHO"[3]. The defining criteria of these metabolic states differ significantly between studies and are defined under highly subjectivity levels, nonetheless insulin sensitivity

Table 3. Psychobiologic Habits according to metabolic phenotypes. Maracaibo city, Venezuela.

	(HNW) A		(MUNW) B		(MHO) C		(MUO) D			A vs. B	A vs. C	A vs. D	B vs. C	B vs. D	C vs. D
	n	%	n	%	n	%	n	%	$\chi 2$ (p)*	p**	p**	p**	p**	p**	p**
Smoking Habit									30.91 (<0.001)						
No Smoker	415	77.7	44	68.8	154	72.6	261	63.5		NS	NS	<0.05	NS	NS	NS
Smoker	72	13.5	12	18.8	30	14.2	67	16.3		NS	NS	NS	NS	NS	NS
Past Smoker	47	8.8	8	12.5	28	13.2	83	20.2		NS	NS	<0.05	NS	NS	NS
Physical Activity Work Sphere									0.49 (0.92)						
Inactive	408	75.8	50	78.1	159	74.6	307	74.7		NS	NS	NS	NS	NS	NS
Active	130	24.2	14	21.9	54	25.4	104	25.3		NS	NS	NS	NS	NS	NS
Physical Activity Transport Sphere									26.93 (<0.001)						
Inactive	163	30.6	19	30.2	87	41.0	188	46.4		NS	<0.05	<0.05	NS	NS	NS
Active	369	69.4	44	69.8	125	59.0	217	53.6		NS	<0.05	<0.05	NS	NS	NS
Physical Activity Household Sphere									13.69 (<0.01)						
Inactive	125	23.2	15	23.4	75	35.2	126	30.7		NS	<0.05	NS	NS	NS	NS
Active	413	76.8	49	76.6	138	64.8	285	69.3		NS	<0.05	NS	NS	NS	NS
Physical Activity Leisure Sphere									19.75 (<0.001)						
Inactive	305	56.7	37	57.8	134	62.9	290	70.6		NS	NS	<0.05	NS	NS	NS
Active	233	43.3	27	42.2	79	37.1	121	29.4		NS	NS	<0.05	NS	NS	NS
Total	**538**	**100**	**64**	**100**	**213**	**100**	**411**	**100**							

HNW (Healthy Normal Weight); MUNW (Metabolically Unhealthy Normal Weight); MHO (Metabolically Healthy Obese); MUO (Metabolically Unhealthy Obese).
* Chi-Square Test. ** Z-test of proportions.

and lipid profile are often used to define healthy and unhealthy phenotypes[22–24].

Giving this criteria and methods discrepancy, such as the psychobiologic, sociodemographic, and genetic patterns according to latitudes, the phenotype frequency presents high variability[25]. This could bias the study by selecting predetermined variables and cut-off points to consider an individual as healthy or unhealthy. In this sense, data mining techniques were proposed to avoid potential bias. The program would group subjects according to spontaneous tendencies and biologic behavior of related variables.

Applied studies in Asia reported a prevalence of 8.7%–13.07% and 3.9%–15.5% for MUNW and MHO phenotypes, respectively[26,27]. Likewise, studies conducted in Europe reported frequencies ranging between 18.9% and 45.8% for the MUNW phenotype, and between 2.1% and 18.5% for the MHO phenotype[28–30]; a similar variability was observed in American research studies[31,32]. Latin American reports are scant, however Fanghanel *et al.*[33] showed a 5.8% prevalence of the MUNW phenotype for the Mexico City, similar to the one showed in the present study, whereas contrasting the obese phenotypes the Maracaibo population exhibited the highest prevalence of MHO subjects (17% vs 10.8% of the Mexican population).

The atypical metabolic phenotypes, as MUNW and MHO, tend to be observed in females with more frequency[32,34]. However, the present study reported these phenotypes were more frequent in males. Significant difference between sexes was found in

Table 4. Endocrine-Metabolic Alterations according to metabolic phenotypes Maracaibo city, Venezuela.

	(HNW) A		(MUNW) B		(MHO) C		(MUO) D			A vs. B	A vs. C	A vs. D	B vs. C	B vs. D	C vs. D
	n	%	n	%	n	%	n	%	$\chi 2$ (*p*)*	*p***	*p***	*p***	*p***	*p***	*p***
HOMA2-IR									727.9 (<0.0001)						
<2	434	80.7	13	20.3	193	90.6	12	2.9		<0.05	NS	<0.05	NS	<0.05	<0.05
≥2	104	19.3	51	79.7	20	9.4	399	97.1		<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
Hypertension									182.22 (<0.0001)						
Absent	331	87.3	32	82.1	53	43.1	96	39.8		NS	<0.05	<0.05	<0.05	<0.05	NS
Present‡	48	12.7	7	17.9	70	56.9	145	60.2		NS	<0.05	<0.05	<0.05	<0.05	NS
Triglycerides									142.09 (<0.0001)						
Normal	487	90.5	42	65.6	153	71.8	235	57.2		<0.05	<0.05	<0.05	NS	NS	<0.05
High	51	9.5	22	34.4	60	28.2	176	42.8		<0.05	<0.05	<0.05	NS	NS	<0.05
HDL-C									44.08 (<0.0001)						
Normal	283	52.6	30	46.9	85	39.9	129	31.4		NS	<0.05	<0.05	NS	NS	NS
Low	255	47.4	34	53.1	128	60.1	282	68.6		NS	<0.05	<0.05	NS	NS	NS
Metabolic Syndrome									339.38 (<0.0001)						
Absent	472	87.7	45	70.3	100	46.9	126	30.7		<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
Present	66	12.3	19	29.7	113	53.1	285	69.3		<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
Total	**538**	**100**	**64**	**100**	**213**	**100**	**411**	**100**							

HNW (Healthy Normal Weight); MUNW (Metabolically Unhealthy Normal Weight); MHO (Metabolically Healthy Obese); MUO (Metabolically Unhealthy Obese).

* Chi-Square Test.

** Z-test of proportions.

‡Personal history and Diagnosis in the Study.

the MUNW group, similar to the study by Hinnouko *et al.*[35]. Smoking habit, age, and physical activity values, were discovered as influencing factors in these findings.

In the same manner, multiple studies have reported that healthy phenotype prevalence decreases with age[27,29], but in our population an increase was observed in the frequency of MHO individuals older than 30 years old. Yoo *et al.*[36] did not report differences in this phenotype prevalence between subjects older and younger than 35 years. Regarding the MUNW phenotype in the Maracaibo population, a higher frequency was found in subjects younger than 30 years. A considerable part of epidemiologic studies that evaluate this association possessed samples conformed by subjects older than 35 years. This may limit the establishment of a tendency in frequency of healthy phenotypes according to age. Similarly, factors such as ethnicity from African descendants[37] and socioeconomical status[38] have been related to the presence of atypical phenotypes, but no relationship was found between these variables in Maracaibo population.

Table 5. Clinical and biochemical characteristics according to metabolic phenotypes. Maracaibo city, Venezuela.

	HNW [A]		MUNW [B]		MHO [C]		MUO [D]			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	*p**	*Pos-hoc Analysis* §
Age (years)	32,5	14,7	34,1	16,5	42,9	13,5	43,1	13,2	<0.001	C and D > A and B
Body Mass Index (Kg/m²)	21,9	2,1	22,9	1,7	34,5	4,7	35,4	5,6	<0.001	C and D > A and B
Waist Circunference (cm)										
Female	79,3	8,2	77,2	7,1	104,4	10,6	105,5	10,1	<0.001	C and D > A and B
Male	81,5	6,9	86,9	7,6	109,2	11,9	116,0	15,3	<0.001	C and D > A and B
HOMA2-βcell	127,2	40,4	204,5	88,2	118,9	37,0	188,7	80,8	<0.001	B > A and C
HOMA2-S	81,9	44,6	41,0	27,3	80,6	36,9	32,8	10,5	<0.001	A and C > B and D
HOMA2-IR	1,5	0,5	3,2	1,6	1,4	0,4	3,5	1,6	<0.001	B and D > A and C
Insulin (µU/mL)	9,9	3,6	22,3	11,9	9,6	2,9	23,7	11,8	<0.001	B and D > A and C
Glucose (mg/dL)	89,3	10,1	94,9	22,7	91,9	11,3	103,2	28,9	<0.001	D > A, B and C
Total Cholesterol (mg/dL)	174,9	38,8	180,1	44,9	196,5	52,3	200,8	45,4	<0.001	D and C > A
Triglycerides (mg/dL) ¶	73.4	53.0–106.0	99.1	67.9–209.0	107.7	75.0–164.0	135.2	97.0–193.0	<0.001	C and D > A and B
HDL-C (mg/dL)										
Female	49,3	11,8	51,6	11,5	45,6	13,0	44,1	11,5	<0.001	B > C and D
Male	46,0	11,2	39,5	11,8	40,2	9,9	36,7	8,5	<0.001	A > B, C and D
VLDL-C (mg/dL)	17,1	9,3	31,0	28,5	26,7	20,4	32,5	21,5	<0.001	B and D > A
LDL-C (mg/dL)	109,8	34,5	106,4	40,2	126,3	35,1	128,0	37,2	<0.001	C and D > A and B
Lipoprotein(a) (mg/dL)	26,1	14,0	22,2	14,7	28,7	13,4	29,3	14,1	<0.001	C and D > B
hs-C Reactive Protein (mg/L) ¶	0.297	0.070–0.598	0.235	0.099–0.580	0.435	0.177–0.814	0.562	0.195–1.222	<0.001	C and D > A and B
Non HDL Cholesterol	126,9	38,6	135,3	45,5	153,8	51,9	160,3	45,1	<0.001	C and D > A and B
Triglycerides/ HDL-C Index¶	1.5	1.0–2.4	2.4	1.4–5.5	2.8	1.7–4.1	3.5	2.3–5.5	<0.001	C and D > A
Visceral Adiposity Index¶	1.7	0.7–1.8	1.6	0.9–3.3	1.8	1.2–2.9	2.4	1.7–3.9	<0.001	D > A, B and C
Systolic Blood Pressure (mmHg)	111,9	13,3	115,2	15,3	125,3	18,4	125,6	17,3	<0.001	C and D > A and B
Diastolic Blood Pressure (mmHg)	71,7	9,4	73,9	10,9	81,5	12,3	81,9	11,2	<0.001	C and D > A and B

HNW (Healthy Normal Weight); MUNW (Metabolically Unhealthy Normal Weight); MHO (Metabolically Healthy Obese); MUO (Metabolically Unhealthy Obese).

SD=Standar Deviation;

* One-way ANOVA Test.

¶ As Median (p25–p75th) Comparison: Kruskal Wallis Test.

§ Pos-hoc Tukey analysis for means and ANOVA with Bonferroni correction for medians. Statistical significant difference (p<0.05).

Table 6. Logistic regression model for metabolic phenotypes and coronary risk categories. Maracaibo city, Venezuela.

	Crude Odds Ratio (IC 95%[a])	*p*[b]	Adjusted Odds Ratio* (IC 95%[a])	*p*[b]
Metabolic Phenotypes				
Metabolically Healthy Normal Weight	1,00	-	1,00	-
Metabolically Unhealthy Normal Weight	3,41 (1,46 - 7,98)	< 0,01	2.24 (0,89 - 5.56)	0,08
Metabolically Healthy Obese	2,26 (1,40 - 3,64)	< 0,01	1.85 (1.11 - 3.09)	0,02
Metabolically Unhealthy Obese	2,85 (1,89 - 4,29)	< 0,01	2.09 (1.34 - 3.28)	< 0,01

a Confidence Interval (95%); **b** Level of significance

Dependent Variable: Coronary risk: <5% in 10 years vs ≥5% in 10 years

***** Adjusted Model for: sex, age, ethnic group, socioeconomic status, smoking habit, physical activity in leisure dimension according to IPAQ, high TAG, and metabolic phenotypes.

One of the greatest enigmas formulated in relation to the atypical metabolic phenotypes, is focused on its conditioning factors. Psychobiologic habits have been considered key elements in comprehension of its biology and behavior related to time. Diniz *et al.*[39] found a significant association between healthy metabolic phenotypes with absence of smoking habit, also with increased PA levels, such as the present study. Ortega *et al.*[40] reported that MHO subjects present with better cardiorespiratory fitness profiles than their unhealthy counterpart, and by adjusting for this variable the MHO individuals showed less mortality. Other studies report that the phenotypes progression from health to unhealthiness is not related to the smoking habit, alcohol, or quantified PA through indirect methods[30] and depends fundamentally on abdominal circumference and visceral adiposity increment.

Regarding to cardiometabolic profiles, our study showed evidence of significantly higher HOMA2-βcell values in all of the unhealthy phenotypes, described previously by the NHANES study[41] and by Madeira *et al.*[42]. Also higher HOMA2-IR and a lower HOMA2-S demonstrate again the importance to define metabolic states in lean and obese individuals. They could also elevate the risk of developing T2DM and CVD in the unhealthy phenotypes, given their hyper functioning pancreatic beta cell and hyperinsulinemia[43].

MHO subjects present with lower HOMA2-IR and higher TAG, LDL-C, PAS, PAD, and hs-CRP levels. In contrast to lean subjects, MHO has higher VAI. The latter constitutes an initial obesity state, without a significant risk of T2DM and CVD in the short term (7–11 years)[44], but there is in the long term (>16–30 years)[45]. The natural history of the MHO is variable, only 16% of MHO individuals stay on that status without alteration for the following 7–8 years[46]. Those who progress to an unhealthy state present a higher risk of high blood pressure, low-grade inflammation, bad metabolic control and high TAG[30]. In spite of the metabolic "benign" state of the MHO adipose tissue, non-metabolic complications of obesity, do not exclude these subjects from getting T2DM, CVD, and chronic diseases associated with obesity in the future[34,35].

Healthy obese individuals must be classified in categories with higher risk of a coronary event compared to lean subjects. This is consistent with previous reports related to metabolic phenotypes and CVD, suggesting that healthy obese subjects have a higher risk profile in comparison to those with lower BMI[36]; as well as an increased risk for CVD[47] and metabolic disorders such as fatty liver and low-grade inflammation[7]. Given the above, a profound evaluation of these patients is recommended. This includes not only obese subjects but also those who are overweight, which can go unnoticed in a routine consultation and CVD could be subclinical; as it has been demonstrated by Khan *et al.* in 475 women from the SWAN study[48].

Finally, despite the fact that our report presents a novel method to classify healthy and unhealthy subjects, the classification was made based on anthropometric measures due to the lack of availability of large-scale imaging studies to determine visceral adiposity in our region. Likewise, it is important to mention the difficulty to follow-up these individuals, the latter would show the atypical phenotype stability related to time, as well as the incidence of T2DM and CVD, this was another limitation of our study. In addition our study lacks nutritional data. For this reason, a through and constant evaluation of subjects with atypical metabolic phenotypes is recommended, given their demonstrated unsteadiness in time, and associated non metabolic comorbidities observed especially in the MHO individuals.

Data availability

Underlying data

Salazar, Juan; Bermudez, Valmore (2021): Biochemical and clinical characterization of metabolic phenotypes: a cross-sectional study from Maracaibo city, Venezuela _Dataset.xlsx. figshare. Dataset. https://doi.org/10.6084/m9.figshare.14213654.v1[49]

Ethics and consent

The study was approved by the Bioethics Committee of the Endocrine and Metabolic Research Center – University of Zulia (approval number: BEC-006-0305). This ethical approval included all future studies that used the data from the Maracaibo City Metabolic Syndrome Prevalence Study (MMSPS). All participants signed written a informed consent for participation in the study before being questioned and physically examined by a trained team.

Abbreviations

CVD: cardiovascular disease

HDL-C: High Density Lipoprotein - Cholesterol

HNW: healthy normal-weight

HOMA: Homeostasis Model Assesment

HTN: hypertension

hs-CRP: high-sensitivity C-Reactive Protein

IR: insulin resistance

LDL-C: Low Density Lipoprotein – Cholesterol

MAP: mean arterial pressure

MET: Metabolic Equivalent

MMSPS: Maracaibo City Metabolic Syndrome Prevalence Study

MHO: metabolically healthy obese

MS: Metabolic Syndrome

MUNW: metabolically unhealthy normal-weight

MUO: metabolically unhealthy obese

PA: Physical activity

SD: standard deviation

TAG: triglycerides

T2DM: Type 2 Diabetes Mellitus

VAI: Visceral Adiposity Index

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The authors carried out a cross-sectional sub-analysis on The Maracaibo City Metabolic Syndrome Prevalence Study, to evaluate biochemical and clinical characteristics of metabolic phenotypes in Maracaibo city. The prevalence of healthy normal weight, unhealthy normal weight, healthy obese and unhealthy obese subjects was obtained. “Metabolic Unhealthy Normal-Weight” and “Metabolic Healthy Obese” are interesting but has been controversial concepts, which makes the current study potentially important.

It is interesting to note that the tendency of atypical metabolic phenotypes in either male or female is different in the current cohort than the previously report ones. Could the authors elaborate more in the discussion section in terms of the possible reason and the clinical implications lying behind?

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
I cannot comment. A qualified statistician is required.

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Endocrine disorders, Obesity, Insulin resistance

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 31 March 2021

https://doi.org/10.5256/f1000research.29764.r82112

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Manfred J. Müller
Institute of human nutrition and food science, Christian Albrechts Universität zu Kiel, Kiel, Germany

I still feel that the authors did not specifically address my concerns. To refer to other authors (and their papers) who went the same way of thinking cannot provide an opportunity to do a next step forward. The arbitrary nature of statistically defined phenotypes should be mentioned in the discussion of the paper. It is obvious that we need a functional approach rather than a static and statistical approach to address metabolic phenotypes. Metabolism is a process which cannot be characterized by e.g. assessing the plasma levels of metabolites and hormones in a basal state. By contrast, metabolism is about fluxes and substrate turnovers which again are related to systemic outcomes (e.g., body temperature, heart rate, blood pressure etc). The concept of functional body composition' provides a useful framework of future research. This has to be addressed in the discussion section. Resisting on a conventional approach is not solution-oriented research.

Repeating and repeating again that many scientists still use crude anthropometric variables cannot be taken as a justification to go on using them. Faced with the present methodological advances it is questionable to go on to apply outdated methods (i.e., anthropometry). Modern techniques used for body composition analysis are neither cumbersome nor expensive. They are already established in huge population studies like NHANES and the UK Biobank Study. If clinicians still insist to use the BMI and wc they are after now. This is a matter of fact. Again, referring to other authors who still work on BMI and wc cannot be taken as a justification to be after.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Metabolism, phenotyping

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Version 2

Reviewer Report 03 September 2020

https://doi.org/10.5256/f1000research.19357.r70666

Manfred J. Müller
Institute of human nutrition and food science, Christian Albrechts Universität zu Kiel, Kiel, Germany

My major concern is about the general idea of a metabolically healthy obese subjects. This is an arbitrary rather than a biological phenotype. BMI (and also fat mass) have a limited precision to estimate metabolic risks, i.e., the respective ROC estimates are around 0.7. Since obesity is about categorization (based on observational data on the association between BMI and mortality risk) the finding that about 30% of obese subjects have no measurable metabolic risks question that clinical categorization rather than generating a specific metabolic phenotype worthwhile to study in detail. Thus, the true message of the present paper should be about a metabolically based categorization of the BMI. To get the idea the authors are referred to e.g., Obes Sci & Pract 2017[1].

References

1. Hübers M, Pourhassan M, Braun W, Geisler C, et al.: Definition of new cut-offs of BMI and waist circumference based on body composition and insulin resistance: differences between children,

adolescents and adults.*Obes Sci Pract*. **3** (3): 272-281 PubMed Abstract | Publisher Full Text

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Metabolism, phenotyping

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Reviewer Report 22 January 2019

https://doi.org/10.5256/f1000research.19357.r42581

Víctor A. Cortes
Department of Nutrition, Diabetes and Metabolism, School of Medicine, Pontifical Catholic University of Chile (UC), Santiago, Chile

I believe the current version of the paper fully addresses my comments.

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Partly

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 19 July 2018

https://doi.org/10.5256/f1000research.15107.r35881

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Víctor A. Cortes
Department of Nutrition, Diabetes and Metabolism, School of Medicine, Pontifical Catholic University of Chile (UC), Santiago, Chile

The authors aimed to estimate the prevalence of “atypical metabolic phenotypes” i.e. lean metabolically unhealthy and obese metabolically healthy individuals in the city area of Maracaibo, Venezuela. For that, they analyzed previously generated data from a cross-sectional city-wide health survey (MMSPS), grouping individuals in three BMI categories (normal weight, overweight and obese) and in two “metabolic health” categories (healthy and unhealthy).

Overall, this study is incremental, reporting no new scientific information on the metabolic phenotypes whatsoever. Its relevance relay on the fact that is methodologically correct study of a Latin American population, which is largely underrepresented in the international literature.

Nevertheless, there are several specific caveats that must be addressed before the article be suitable for indexing:

Abstract:
Methodololgy:

1. It must tell the source of the sample to make clear that is a city-wide health survey.
2. It must indicate what was the specific criteria for this clustering individuals in healthy/unhealthy categories. It is not enough to tell that is was made upon a 2-step clustering analysis.

Results:

1. It should be re written to clearly indicate the frequency of each phenotype category and indicate if there were differences between the sexes in this distribution and the OR for casrdiovascular risk factors or diseases.
2. It must indicate what is the difference between unhealthy lean and unhealthy normal-weight individuals

Conclusions: There are no reasons to suppose that individuals of Maracaibo city will have no "atypical metabolic phenotypes" as the rest of the world populations, thus the authors should rephrase this sentence to make more scientifically sound. Also, the conclusion relative to the increased cardiovascular risk of "healthy obese" individuals should be better explained since it cannot be derived from the data reported in the
Results section of the abstract.

Introduction:
The phrase: "For this reason, the actual clinical practice catalogues an obese patient as an "unhealthy" patient and a lean patient is considered "healthy", should be modified to make its medical meaning clearer, because it is evident for everybody that many lean people are unhealthy.

Also, the paper will gain interest if the authors comment what is the importance of researching the "atypical phenotypes"in general. For example, is there any evidence that these individuals can be misclassified in their cardiometabolic risk based solely in the BMI?

Finally, it is important that the authors comment the extent to what Maracaibo city population is representative of other Latin American populations. For international readers will be interesting to learn that American populations are extremely heterogenous in both genetic and cultural aspects.

Materials and methods:
"Population selection": this whole methodological section is cryptic and is basically a summary of the published in the reference 9. I suggest to re write it to make more understandable for general readers. Specifically, it must be justified why the authors did choose not to use more a conventional definition of metabolic health, such as the metabolic syndrome definition used by ATP III guidelines.

"Physical activity": it should be improved the explanation of what is the relevance and connection of table 1 with the rest of the paper. Also, in this table there is no quantitative definition of the "Work domain" and "lower/upper limit" categories. Information of the proportion of each category over the overall would be useful to summarize these data.

"Calibration of the Framingham-Wilson equation and coronary risk categorization for the

population of Maracaibo city": the authors must explain what asymptomatic angina is, since medically angina is a symptom by itself.

Results:
Table 2: change "Indian-american" for "native American", if its corresponds since "Indian" correspond to India nationals

"Metabolic phenotypes and biologic-anthropometric variables" section: Since all the variables in this table are statistically different, a post test comparing individual groups should be important to make sense of the noted global differences.

Also, a better description and explanation of these particular results is required in the main text.

"Metabolic phenotypes and coronary risk classification" section: the meaning of the first phrase must be clarified since only obese individuals showed increased OR: other comparisons were not statistically significant with the adjusted model, thus were not different.

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
I cannot comment. A qualified statistician is required.

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Basic and clinical research on adipose tissue disorders, diabetes, dyslipidemia and fatty liver

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.