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

Valmore Bermudez, Joselyn Rojas, Juan Salazar, Maria Sofia Martinez, Luis Carlos Olivar, Maria Jose Calvo, Andres Mindiola, Roberto Añez, Sandra Wilches-Duran, Marcos Cerda, Modesto Graterol, Rosemily Graterol, Juan Diego Hernandez, Carlos Garicano, Manuel Velasco

1Grupo de Investigación Altos Estudios de Frontera (ALEF), Universidad Simón Bolívar, Cucuta, Colombia
2Endocrine and Metabolic Diseases Research Center, The University of Zulia, Maracaibo, Venezuela
3Pulmonary and Critical Care Medicine Department, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, USA
4Geriatric Research Education and Clinical Center (GRECC), U.S Department of Veterans Affairs, Miami, FL, USA
5Department of Pharmacology, “JM Vargas” Medical School, Central University of Venezuela, Caracas, Venezuela

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
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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**Corresponding authors:** Valmore Bermudez (valmore@gmail.com), Juan Salazar (juanjsv18@hotmail.com)

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Introduction

Obesity is considered an entity with major morbi-mortality in the world since the end of the 20th century. Multiple 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). 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”. Around 20 years later, Ferrannini et al. observed that a group of certain obese non-diabetic 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.

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. Years later, Ruderman et al. introduced the “Metabolically Unhealthy Normal-Weight” phenotype attributed to lean individuals with metabolic alterations associated to obesity.

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. Despite the wide heterogeneity observed in our region influenced by 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.

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. 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 to 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. 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.

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/height²) was applied, expressing the results as kg/m². Obesity was classified applying the WHO criteria based on the BMI value. Finally, WC was measured.
using calibrated measuring tape in accordance to the anatomical landmarks proposed by the USA National Institutes of Health protocol\(^1\).

**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 für Biochemica und Diagnostica mbH). LDL-C and VLDL-C levels were calculated applying the Friedewald formulas\(^1\). 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\(^1\), the HOMA-2-IR model proposed by Levy et al. was utilized 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.\(^1\). The Metabolic Syndrome (MS) diagnosis was done using the Harmonizing-2009 consensus criteria\(^1\).

**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\(^9\). 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\(^\text{th}\) percentile–75\(^\text{th}\) 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 $\chi^2$ 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. $\chi^2$=22.53, p<0.001). Likewise, a statistically significant association was found between age groups and metabolic phenotypes ($\chi^2$= 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; Metabolically Unhealthy Normal-Weight: n=64 (5.2%)  

**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.
Analysis of the smoking habit showed that among the total group of patients, 25.3% were past smokers, whereas 22.0% were current smokers (p = 0.0001). The highest percentage of MHNW patients were past smokers (25.6%), with a significantly lower percentage (12.3%) of MUO smokers (p<0.01). Regarding the smoking habit, a significant association was found between smoking habit and PA (χ²=26.93, p<0.001) and leisure activities (χ²=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 (χ²=44.08; p<0.0001) and HTN (χ²=182.22, p<0.0001).

Metabolic phenotypes and psychobiologic habits
Initially, in relation to the smoking habit, the non-smokers were the most frequent group (χ²=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 (χ²=26.93; p<0.001) and leisure activities (χ²=19.75; p<0.001) (Table 3).

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

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</table>

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”. 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.

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<tr>
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</table>

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.

Giving this criteria and methods discrepancy, such as the psychobiologic, sociodemographic, and genetic patterns according to latitudes, the phenotype frequency presents high variability. 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.

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; a similar variability was observed in American research studies. Latin American reports are scant, however Fanghanel et al. 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. 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.

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<td>46.9</td>
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</tr>
<tr>
<td>Present</td>
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<td>19</td>
<td>29.7</td>
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<td>285</td>
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</tr>
<tr>
<td>Total</td>
<td>538</td>
<td>100</td>
<td>64</td>
<td>100</td>
<td>213</td>
<td>100</td>
<td>411</td>
<td>100</td>
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</table>

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.

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 30 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.

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<tr>
<td><strong>Age (years)</strong></td>
<td>32.5 ± 14.7</td>
<td>34.1 ± 16.5</td>
<td>42.9 ± 13.5</td>
<td>43.1 ± 13.2</td>
<td>&lt;0.001</td>
<td>C and D &gt; A and B</td>
</tr>
<tr>
<td><strong>Body Mass Index (Kg/m²)</strong></td>
<td>21.9 ± 2.1</td>
<td>22.9 ± 1.7</td>
<td>34.5 ± 4.7</td>
<td>35.4 ± 5.6</td>
<td>&lt;0.001</td>
<td>C and D &gt; A and B</td>
</tr>
<tr>
<td><strong>Waist Circumference (cm)</strong></td>
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</tr>
<tr>
<td>Female</td>
<td>79.3 ± 8.2</td>
<td>77.2 ± 7.1</td>
<td>104.4 ± 10.6</td>
<td>105.5 ± 10.1</td>
<td>&lt;0.001</td>
<td>C and D &gt; A and B</td>
</tr>
<tr>
<td>Male</td>
<td>81.5 ± 6.9</td>
<td>86.9 ± 7.6</td>
<td>109.2 ± 11.9</td>
<td>116.0 ± 15.3</td>
<td>&lt;0.001</td>
<td>C and D &gt; A and B</td>
</tr>
<tr>
<td><strong>HOMA2-β-cell</strong></td>
<td>127.2 ± 40.4</td>
<td>204.5 ± 88.2</td>
<td>118.9 ± 37.0</td>
<td>188.7 ± 80.8</td>
<td>&lt;0.001</td>
<td>B &gt; A and C</td>
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<td><strong>HOMA2-S</strong></td>
<td>81.9 ± 44.6</td>
<td>41.0 ± 27.3</td>
<td>80.6 ± 36.9</td>
<td>32.8 ± 10.5</td>
<td>&lt;0.001</td>
<td>A and C &gt; B and D</td>
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<tr>
<td><strong>HOMA2-IR</strong></td>
<td>1.5 ± 0.5</td>
<td>3.2 ± 1.6</td>
<td>1.4 ± 0.4</td>
<td>3.5 ± 1.6</td>
<td>&lt;0.001</td>
<td>B and D &gt; A and C</td>
</tr>
<tr>
<td><strong>Insulin (µU/mL)</strong></td>
<td>9.9 ± 3.6</td>
<td>22.3 ± 11.9</td>
<td>9.6 ± 2.9</td>
<td>23.7 ± 11.8</td>
<td>&lt;0.001</td>
<td>B and D &gt; A and C</td>
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<tr>
<td><strong>Glucose (mg/dL)</strong></td>
<td>89.3 ± 10.1</td>
<td>94.9 ± 22.7</td>
<td>91.9 ± 11.3</td>
<td>103.2 ± 28.9</td>
<td>&lt;0.001</td>
<td>D &gt; A, B and C</td>
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<tr>
<td><strong>Total Cholesterol (mg/dL)</strong></td>
<td>174.9 ± 38.8</td>
<td>180.1 ± 44.9</td>
<td>196.5 ± 52.3</td>
<td>200.8 ± 45.4</td>
<td>&lt;0.001</td>
<td>D and C &gt; A</td>
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<tr>
<td><strong>Triglycerides (mg/dL)</strong></td>
<td>73.4 (53.0–106.0)</td>
<td>99.1 (67.9–209.0)</td>
<td>107.7 (75.0–164.0)</td>
<td>135.2 (97.0–193.0)</td>
<td>&lt;0.001</td>
<td>C and D &gt; A and B</td>
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<td><strong>HDL-C (mg/dL)</strong></td>
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</tr>
<tr>
<td>Female</td>
<td>49.3 ± 11.8</td>
<td>51.6 ± 11.5</td>
<td>45.6 ± 13.0</td>
<td>44.1 ± 11.5</td>
<td>&lt;0.001</td>
<td>B &gt; C and D</td>
</tr>
<tr>
<td>Male</td>
<td>46.0 ± 11.2</td>
<td>39.5 ± 11.8</td>
<td>40.2 ± 9.9</td>
<td>36.7 ± 8.5</td>
<td>&lt;0.001</td>
<td>A &gt; B, C and D</td>
</tr>
<tr>
<td><strong>VLDL-C (mg/dL)</strong></td>
<td>17.1 ± 9.3</td>
<td>31.0 ± 28.5</td>
<td>26.7 ± 20.4</td>
<td>32.5 ± 21.5</td>
<td>&lt;0.001</td>
<td>B and D &gt; A</td>
</tr>
<tr>
<td><strong>LDL-C (mg/dL)</strong></td>
<td>109.8 ± 34.5</td>
<td>106.4 ± 40.2</td>
<td>126.3 ± 35.1</td>
<td>128.0 ± 37.2</td>
<td>&lt;0.001</td>
<td>C and D &gt; A and B</td>
</tr>
<tr>
<td><strong>Lipoprotein(a) (mg/dL)</strong></td>
<td>26.1 ± 14.0</td>
<td>22.2 ± 14.7</td>
<td>28.7 ± 13.4</td>
<td>29.3 ± 14.1</td>
<td>&lt;0.001</td>
<td>C and D &gt; B</td>
</tr>
<tr>
<td><strong>hs-C Reactive Protein (mg/L)</strong></td>
<td>0.297 (0.070–0.598)</td>
<td>0.235 (0.099–0.580)</td>
<td>0.435 (0.177–0.814)</td>
<td>0.562 (0.195–1.222)</td>
<td>&lt;0.001</td>
<td>C and D &gt; A and B</td>
</tr>
<tr>
<td><strong>Non HDL Cholesterol</strong></td>
<td>126.9 ± 38.6</td>
<td>135.3 ± 45.5</td>
<td>153.8 ± 51.9</td>
<td>160.3 ± 45.1</td>
<td>&lt;0.001</td>
<td>C and D &gt; A and B</td>
</tr>
<tr>
<td><strong>Triglycerides/ HDL-C Index†</strong></td>
<td>1.5 ± 1.0–2.4</td>
<td>2.4 ± 1.4–5.5</td>
<td>2.8 ± 1.7–4.1</td>
<td>3.5 ± 2.3–5.5</td>
<td>&lt;0.001</td>
<td>C and D &gt; A</td>
</tr>
<tr>
<td><strong>Visceral Adiposity Index†</strong></td>
<td>1.7 ± 0.7–1.8</td>
<td>1.6 ± 0.9–3.3</td>
<td>1.8 ± 1.2–2.9</td>
<td>2.4 ± 1.7–3.9</td>
<td>&lt;0.001</td>
<td>D &gt; A, B and C</td>
</tr>
<tr>
<td><strong>Systolic Blood Pressure (mmHg)</strong></td>
<td>111.9 ± 13.3</td>
<td>115.2 ± 15.3</td>
<td>125.3 ± 18.4</td>
<td>125.6 ± 17.3</td>
<td>&lt;0.001</td>
<td>C and D &gt; A and B</td>
</tr>
<tr>
<td><strong>Diastolic Blood Pressure (mmHg)</strong></td>
<td>71.7 ± 9.4</td>
<td>73.9 ± 10.9</td>
<td>81.5 ± 12.3</td>
<td>81.9 ± 11.2</td>
<td>&lt;0.001</td>
<td>C and D &gt; A and B</td>
</tr>
</tbody>
</table>

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).
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. 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. 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 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 and by Madeira et al. 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.

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), but there is in the long term (>16–30 years). 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. Those who progress to an unhealthy state present a higher risk of high blood pressure, low-grade inflammation, bad metabolic control and high TAG. 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.

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; as well as an increased risk for CVD and metabolic disorders such as fatty liver and low-grade inflammation. 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.

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 thorough 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.

<table>
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<tr>
<td><strong>Metabolic Phenotypes</strong></td>
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<tr>
<td><strong>Crude Odds Ratio (IC 95%)</strong></td>
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<tr>
<td><strong>Adjusted Odds Ratio (IC 95%)</strong></td>
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<tr>
<td><strong>p</strong></td>
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<td><strong>p</strong></td>
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<tr>
<td>Metabolically Healthy Normal Weight</td>
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<td>Metabolically Healthy Obese</td>
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<tr>
<td>Metabolically Unhealthy Normal Weight</td>
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<td>Metabolically Unhealthy Obese</td>
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<tr>
<td>a Confidence Interval (95%); b Level of significance</td>
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<tr>
<td>Dependent Variable: Coronary risk: &lt;5% in 10 years vs ≥5% in 10 years</td>
</tr>
<tr>
<td>* Adjusted Model for: sex, age, ethnic group, socioeconomic status, smoking habit, physical activity in leisure dimension according to IPAQ, high TAG, and metabolic phenotypes.</td>
</tr>
</tbody>
</table>
Data availability
Underlying data

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 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 Assessment
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

References
Reference Source

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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.

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.
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.

References

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

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Victor 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.
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:**

**Methodology:**

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 cardiovascular 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.

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