Non-HDL cholesterol is better than LDL-c at predicting atherosclerotic cardiovascular disease risk factors clustering, even in subjects with near-to-normal triglycerides: A report from a Venezuelan population [version 1; peer review: 1 approved, 1 approved with reservations]

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Abstract

Background: Non-high density lipoprotein cholesterol (non-HDL-c) has emerged as an important tool in primary prevention of atherosclerotic cardiovascular disease (ASCVD), especially among those at high risk. The main objective of this study was to evaluate the predictive value of non-HDL-c for the coexistence aggregation of multiple ASCVD risk factors and compare this with LDL-c in general subjects with normal or near normal triglycerides from Maracaibo city in Venezuela.

Methods: This is a descriptive, cross-sectional study with a randomized multistage sampling. 2026 subjects were selected for this study, all were adults ≥18 years old of both genders and inhabitants of Maracaibo city, Venezuela. A complete history and physical medical assessment was performed. A multivariate logistic regression model was used to determine the odds ratio (CI95%) for the coexistence of multiple risk factors for ASCVD.

Results: The median (p25-p75) of non-HDL-c was 143 mg/dL (114-174 mg/dL), 52.1% (n=1056) of the sample were women, with a median of 144 mg/dL (115-174 mg/dL) among women and 143 mg/dL (114-174 mg/dL) among men; p=0.740. Individuals ≥50 years old, smokers, those with diabetes, and those with hypertension were significantly more likely to have higher levels of non-HDL-c. The median (p25-p75) of LDL-c was 114 mg/dL (93-144 mg/dL).

Open Peer Review

Reviewer Status

Invited Reviewers

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2 Chandrakala Aluganti Narasimhulu, University of Central Florida, Orlando, USA

Any reports and responses or comments on the article can be found at the end of the article.
among men; \( p=0.740 \). Individuals ≥50 years old, smokers, those with hypertension, obesity, diabetes, high waist circumference and elevated hs-C Reactive Protein, all had higher levels of non-HDL-c. A lower median was observed among those <30 years of age with elevated physical activity levels in their leisure time. Non-HDL-c between 130-159 mg/dL (OR=2.44; CI 95\%=[1.48-4.02]; \( p<0.001 \)) and ≥160 mg/dL (OR=3.28; CI 95\%=[1.72-6.23]; \( p<0.001 \)) was associated with greater risk of coexistent multiple risk factors for ASCVD, albeit LDL-c was not significant in the multivariate model. **Conclusions**: Elevated non-HDL-c was associated with conglomeration of multiple risk factors for ASCVD. This suggests evaluation of non-HDL-c may be of better utility in primary care for early identification of subjects for high risk of ASCVD. Future research might focus on the influence of non-HDL-c in cardiovascular mortality.

**Keywords**

non-HDL-c, LDL-c, cholesterol, ASCVD, risk factor, Coronary Artery Disease

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**Introduction**

Atherosclerotic cardiovascular disease (ASCVD) is the most common cause of morbidity and mortality in the world, representing 31.5% of deaths, with approximately 17.3 million deaths globally\(^1\). Hyperlipidemia plays an important role in the pathogenesis of atherosclerosis by inducing chronic inflammation, arterial plaque formation and remodeling, leading to compromised perfusion. Thankfully, hyperlipidemia remains a modifiable risk factor for ASCVD\(^2\).

Historically, the therapeutic goal for ASCVD risk reduction was to reduce cholesterol levels associated with low density lipoproteins (LDL-c), as elevated quantities have been associated with a higher incidence of ASCVD\(^3\). An important body of evidence, including randomized controlled trials, have demonstrated that statins reduce mortality from ASCVD when used as primary or secondary prevention\(^4\)-\(^6\). Nonetheless, other studies have shown that the risk for future cardiac events remain elevated despite achieving LDL-c goals, suggesting that LDL-c might not be the best estimator of ASCVD in some populations\(^6\),\(^10\).

LDL-c levels only reflect the amount of cholesterol contained within the low density lipoproteins, but does not quantify its quantity, size or structure. Additionally, there are other lipoproteins that possess atherogenic properties, such as very low density lipoproteins (VLDL-c), chylomicrons, and lipoprotein remnants. All these have Apo-B, and can participate in atherogenesis by accumulation in the intima and eliciting pro-inflammatory responses\(^7\). Other disadvantage of using LDL-c is the methodologic limitation of its calculations using Friedewald’s equation, which cannot be used in the setting of hypertriglyceridemia\(^8\). Recall that elevated triglycerides (TGs) can independently increase the risk for ASCVD\(^9\). Therefore, non-high density lipoprotein (HDL) cholesterol has emerged as an alternative predictor of ASCVD.

Non-HDL cholesterol essentially represents the sum of all lipoproteins that have atherogenic properties (LDL, VLDL, IDL, lipoprotein remnant)\(^10\). Studies such as the Emerging Risk Factors Collaboration\(^11\) (N=302,430) suggest that aiming to reduce non-HDL disregarding other lipid parameters might be a new and better approach. This is supported by the fact that patients in this study with elevated non-HDL-c had higher risk of cardiac events (HR=1.50; CI 95%=1.39–1.61) than those with elevated TGs (HR=0.99; CI 95%=0.94–1.05) or with elevated LDL-c (HR=1.38; CI 95%=1.09–1.73). Moreover, non-HDL-c has demonstrated to be a useful predictor for the appearance of metabolic syndrome, which can be of great utility in primary care settings\(^11\). Lastly, non-HDL-c seems to be a better predictor of metabolic syndrome compared with LDL-c, even in patients with TG <400 mg/dL, and the predictive value was independent from central obesity and insulin resistant states\(^12\).

Despite all the advantages of non-HDL-c in order to estimate ASCVD risk, the current practice measurement of non-HDL-c is underused. The objective of this study was to evaluate the predictive value of non-HDL-c for the aggregation of multiple ASCVD risk factors and compare it with LDL-c in general subjects with normal or near normal TGs from Maracaibo municipality in Venezuela.

**Methods**

**Study design and selection of participants**

The Maracaibo City Metabolic Syndrome Prevalence Study (MMSPS) is a descriptive and cross-sectional study carried out by our research group in Maracaibo, Venezuela, with the main goal to determine the prevalence of metabolic syndrome in this population and it’s methodology was described previously\(^13\). For the purpose of the present sub-study, individuals with no determination of fasting insulin level were excluded; thus, a total of 2026 individuals older than 18 years old were included for this investigation. The study was approved by the Bioethics Committee of the Endocrine and Metabolic Diseases Research Center – University of Zulia (approval number: BEC-006-0305). This ethical approval included all future studies that used the data from the MMSPS. All participants signed written consent before being questioned and physically examined by a trained team.

**Clinical evaluation of the participants**

All individuals underwent a full history and physical exam by trained personnel. During the initial interview, personal and family history of premature ASCVD, endocrine and metabolic diseases were explored. Age, gender, as well as social and economic status using Graffar’s scale modified by Mendez-Castellano\(^14\), were recorded. Smoking history was categorized in three different classes: a) current smoker (smoked >100 cigarettes in a lifetime, current smoking, and chronic smoker who stopped for <1 year); b) ex-smoker (smoker who stopped smoking for >1 year); c) non-smoker (never smoked or who smoked <100 cigarettes in a lifetime). Current drinkers were considered to be those having drunk >1 gram a day\(^15\).

Physical activity was assessed by the Long Form of the International Physical Activity Questionnaire (IPAQ)\(^16\). This instrument quantifies the amount of minutes invested in transportation, work, homework (gardening, cleaning), and leisure time. The participants were divided into quintiles based on total Metabolic Equivalents (METs)/min/week scores considering a sedentary person those with a MET score of 0 and those individuals with some degree of physical activity (≥1 MET) were stratified into five groups: very low (Q1), low (Q2), moderate (Q3), high (Q4) and very high (Q5) for a total of six categories. Leisure time was classified as follows: Q1 or very low PA in men<296.999 METs and women <230.999 METs; b) Q2 or low PA in men 297.000–791.999 METs and women 231.000–445.499 METs; c) Q3 or moderate PA in men 792.000–1532.399 METs and in women 445.500–742.499 METs; d) Q4 high PA in men 1532.400–2879.999 METs and in women 742.500–1798.499 METs; and e) Q5 or very high PA in men ≥2879.000 METs and women ≥1798.500 METs.
Blood pressure evaluation

Blood pressure was measured by manual methods using a sphygmomanometer and stethoscope to detect 1st and 5th Korotkoff’s sounds for systolic and diastolic blood pressure, respectively. Participants had a 15 minute resting period before BP determination, they were being seated with both feet on the ground. Measurements were repeated three times in 15 minute intervals. Joint National Committee 7 (JNC7) was used to classify BP as normal BP <120/80 mmHg, prehypertension in those with systolic blood pressure (SBP) 120–139 mmHg and/or diastolic blood pressure (PAD) between 80–89 mmHg, and hypertension when BP is ≥140/90 mmHg\(^2\).

Anthropometric evaluation

Height was determined using a calibrated stadiometer placed on a flat surface. Weight was measured using a digital scale (Tanita, TBF-310 GS Body Composition Analyzer, Tokyo – Japan), with the patient wearing light clothing and barefoot. Body mass index (BMI) was determined using Queteleć’s equation [weight/height\(^2\)], and using World Health Organization criteria participants were deemed normal weight (BMI <25 kg/m\(^2\)), overweight (25.0 – 29.9 kg/m\(^2\)), and obese (≥30.0 kg/m\(^2\))\(^3\).

Waist circumference was measured using a standardized metric belt using the metric system in centimeters and millimeters. An anatomic reference was used to measure waist circumference an equidistant point between the lower border of the ribs and the antero-superior iliac spine, according to the National Institutes of Health of the United States\(^4\). Central obesity was considered if waist circumference was ≥91 cm in women and ≥98 cm in men, according to the specific cut off values proposed for the population of Maracaibo, Venezuela\(^5\).

Laboratory analyses

Antecubital venous sampling was performed after an eight hour period of fasting. Samples were centrifuged and serum was obtained. Levels of glucose, total cholesterol, and TGs were determined using commercial enzymatic and colorimetric ELISA kits (Human Gesellshoft Biochemica and Diagnostica MBH). Glucose levels were interpreted according to the American Diabetes Association 2017 diagnostic criteria as follows: normal glucose <100 m/dL, impaired fasting glucose when fasting glucose is 100–125 mg/dL, and diabetes mellitus when glucose was ≥126 mg/dL\(^6\). Before diagnosing diabetes, a confirmatory test was repeated on a different day. Levels of high sensitive C reactive protein (hs-CRP) were determined using immunoturbidimetric analyses (Human Gesellshoft Biochemica and Diagnostica MBH), and the cut off point for an elevated hs-CRP was ≥0.765 mg/L\(^7\).

Fasting insulin concentration was determined using a commercial kit based on ELISA (DRG International, Inc. USA, New Jersey), with a detection limit of <1 mU/L. Resistance to insulin was calculated by the software HOMA-Calculator v2.2.2 provided by the Oxford Centre for Diabetes Endocrinology and Metabolism. Cutoff value for HOMA2-IR was 2.00\(^8\).

Evaluation of non-HDL cholesterol and LDL-c

Non-HDL cholesterol levels were calculated with the following formula:

\[
\text{Non-HDL-c} = \text{total cholesterol} – \text{HDL-c}
\]

LDL-c were determined using Friedwald formula\(^9\). Cutoff points for non-HDL-c: a) <130 mg/dL; b) 130–159 mg/dL; and c) ≥160 mg/dL. Cutoff points for LDL-c: a) <100 mg/dL; b) 100–129 mg/dL; and c) ≥130 mg/dL\(^10\).

Definition of composite of multiple risk factors

The aggregation of multiple risk factors was considered when one individual presented with two or more of the following:

- Fasting glucose ≥100 mg/dL;
- Blood pressure ≥130/85 mmHg;
- Waist circumference ≥91 cm in females and ≥98 cm in males;
- HOMA2-IR≥2.

Statistical analysis

Qualitative variables were shown as absolute and relative frequencies. Associations between these variables were explored using \(\chi^2\) (Chi square) testing and differences with Z test. Quantitative variables were shown as arithmetic mean ± standard deviation after normality testing was performed using the Geary test. Non-normal distribution variables were logarithmically transformed and analyzed as with parametric testing when normality was achieved. When these variables remained non-normal they were shown as median with inter-quartile ranges (p25–p75\(^8\)). U Mann Whitney test and Kruskal-Wallis test were used for comparisons between two groups and three or more groups, respectively.

A multivariate regression model was created to estimate odds ratio and confidence intervals for prediction of composite of multiple risk factors. The first model was adjusted for age, sex, age group, ethnic group, socio-economic status, literacy, employment status, smoking, alcohol consumption, physical activity during leisure time, hypertension, hs-CRP, LDL-c and non-HDL cholesterol.

SPSS v.21 for Windows (IBM Chicago, IL) was used for statistical analyses and data gathering. We considered results statistically significant at \(p<0.05\).

Results

General characteristics of the sample

From the 2026 participants, 52.1% (n=1056) were female and 47.9% were male (n=846). The mean age was 40.79±15.76 years. Other general features are presented in Table 1. Median non-HDL-c was 143 mg/dL (114–174) mg/dL, with 144 (115–174) mg/dL among females and 143 (114–174) mg/dL in males; \(p=0.740\).
Epidemiology of non-HDL-c: Age, ethnicity, smoking, alcohol and physical activity

Table 2 shows the epidemiology of non-HDL-c according to social and demographic features. Non-HDL-c levels showed an increasing trend with age, from 118 (97–143) mg/dL in those <30 years old, 151 (124–175) mg/dL among those from 30–49 years old and 166 (137–196) mg/dL in >50 years old; *p*<0.001. On the other hand, indigenous Venezuelan populations showed lower non-HDL-c levels (127; 97–151 mg/dL) compared with mixed race (145; 116–175 mg/dL; *p*<0.001). Higher levels of non-HDL-c were found among smokers (151; 118–183 mg/dL) compared with non-smokers or ex-smokers, *p*=0.001. Subjects with very high physical activity exhibited lower non-HDL-c levels 124 (98–160) mg/dL when compared with sedentary subjects [147 (118–175) mg/dL; *p*<0.001]. No significant differences were found when comparing alcohol drinkers and non-drinkers.

Non-HDL-c, chronic diseases and low-grade inflammation: Hypertension, obesity, diabetes and hs-CRP

Table 3 shows non-HDL-c levels according to clinical, metabolic, and anthropometric variables. Non-HDL-c were significantly higher among those with hypertension compared to those with normal blood pressure (159 vs. 132 mg/dL, respectively; *p*<0.001). This behavior was also observed when comparing obese and normal weight individuals (155 vs. 124 mg/dL, respectively; *p*<0.001), type 2 diabetes and non-diabetic individuals (161 vs. 137 mg/dL; *p*<0.001), abdominal obesity and persons with normal waist circumference (154 vs. 132 mg/dL; *p*<0.001), and elevated hs-CRP vs. normal hs-CRP (156 vs. 140 mg/dL; *p*<0.001). Tertile distribution according non-HDL-c and both, clinical and anthropometric variables are shown in Table 4.

Non-HDL-c and composite of multiple risk factors for ASCVD

Figure 1 shows levels of non-HDL-c according to the number of risk factors for ASCVD. Those with any risk factor had a non-HDL-c of 122 (98–146) mg/dL, and 161 (131–192) mg/dL in those with three criteria and 159 (137–195) mg/dL in those with four criteria; *p*<0.001. Table 5 shows a multivariate logistic regression model where levels of non-HDL-c between 130 – 159 mg/dL, (OR=2.59; CI95%: 1.62-4.13; *p*<0.001) and ≥160 mg/dL (OR=3.75; CI95%:2.04-6.91; *p*<0.001), had an inverse probability of presenting a composite of multiple risk factors, while LDL-C was not significantly associated (OR=0.42; CI95%: 0.23-0,95; *p*=0.035).

**Table 1. General characteristics of the sample.**

<table>
<thead>
<tr>
<th></th>
<th>WOMEN (n= 1056)</th>
<th>MEN (n=970)</th>
<th>TOTAL (n=2026)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (Years)</strong></td>
<td>41.06±15.68</td>
<td>38.20±14.89</td>
<td>39.69±15.37</td>
</tr>
<tr>
<td><strong>Weight (Kg)</strong></td>
<td>69.35±16.17</td>
<td>84.58±20.29</td>
<td>76.64±19.77</td>
</tr>
<tr>
<td><strong>Height (meters)</strong></td>
<td>1.58±0.07</td>
<td>1.71±0.07</td>
<td>1.64±0.10</td>
</tr>
<tr>
<td><strong>Body mass index (kg/m²)</strong></td>
<td>27.90±6.23</td>
<td>28.84±6.21</td>
<td>28.35±6.23</td>
</tr>
<tr>
<td><strong>Systolic blood pressure (mmHg)</strong></td>
<td>91.10±13.77</td>
<td>98.76±15.90</td>
<td>94.77±15.31</td>
</tr>
<tr>
<td><strong>Diastolic blood pressure (mmHg)</strong></td>
<td>117.63±17.48</td>
<td>122.15±15.98</td>
<td>119.80±15.98</td>
</tr>
<tr>
<td><strong>Fasting Glucose (mg/dL)</strong></td>
<td>75.56±10.85</td>
<td>79.17±11.52</td>
<td>77.29±11.32</td>
</tr>
<tr>
<td><strong>Fasting insulin (mU/L)</strong></td>
<td>98.65±31.54</td>
<td>99.67±33.94</td>
<td>99.14±32.71</td>
</tr>
<tr>
<td><strong>Total Cholesterol (mg/dL)</strong></td>
<td>2.18±1.37</td>
<td>2.23±1.47</td>
<td>2.21±1.42</td>
</tr>
<tr>
<td><strong>Triacylglycerides (mg/dL)</strong></td>
<td>114.73±44.78</td>
<td>188.07±47.53</td>
<td>191.54±46.22</td>
</tr>
<tr>
<td><strong>HDL-C (mg/dL)</strong></td>
<td>117.16±85.47</td>
<td>146.23±116.50</td>
<td>131.08±102.52</td>
</tr>
<tr>
<td><strong>LDL-C (mg/dL)</strong></td>
<td>46.99±11.86</td>
<td>40.89±11.34</td>
<td>44.07±12.00</td>
</tr>
<tr>
<td><strong>Non HDL-c (mg/dL)</strong></td>
<td>125.07±39.51</td>
<td>120.61±42.33</td>
<td>122.93±40.94</td>
</tr>
</tbody>
</table>

All results are shown as arithmetic mean and standard deviation, except Non HDL-c (median p25–p75%).

**Abbreviations:** HDL-c: High density lipoprotein cholesterol; LDL-c: Low density lipoprotein cholesterol; HOMA: Homeostasis model assessment.

Dataset 1. MMSPS non-HDL and atherosclerotic cardiovascular disease risk factors raw data

http://dx.doi.org/10.5256/f1000research.13005.d19598
### Table 2. Non-HDL-C behavior according to sociodemographic characteristics and some psycho-biological habits.

<table>
<thead>
<tr>
<th></th>
<th>Non-HDL-C (mg/dL) Median (p25–p75)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age Groups (years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>118 (97–143)</td>
<td></td>
</tr>
<tr>
<td>30–49</td>
<td>151 (124–175)</td>
<td></td>
</tr>
<tr>
<td>&gt;50</td>
<td>166 (137–196)</td>
<td></td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mixed</td>
<td>145 (116–175)</td>
<td></td>
</tr>
<tr>
<td>Hispanic white</td>
<td>145 (114–176)</td>
<td></td>
</tr>
<tr>
<td>Afro-venezuelans</td>
<td>134 (108–164)</td>
<td></td>
</tr>
<tr>
<td>Amerindians</td>
<td>127 (97–151)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>147 (124–183)</td>
<td></td>
</tr>
<tr>
<td><strong>Alcohol consumption</strong></td>
<td></td>
<td>0.781</td>
</tr>
<tr>
<td>Yes</td>
<td>142 (114–174)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>144 (114–174)</td>
<td></td>
</tr>
<tr>
<td><strong>Tobacco smoke</strong></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No smoker</td>
<td>139 (110–169)</td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>151 (118–183)</td>
<td></td>
</tr>
<tr>
<td>Former smoker</td>
<td>150 (129–184)</td>
<td></td>
</tr>
<tr>
<td><strong>Physical activity</strong></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(Leisure time dominion)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactive</td>
<td>147 (118–175)</td>
<td></td>
</tr>
<tr>
<td>Very Low</td>
<td>147 (117–178)</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>140 (117–168)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>142 (111–180)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>137 (112–174)</td>
<td></td>
</tr>
<tr>
<td>Very High</td>
<td>124 (98–160)</td>
<td></td>
</tr>
</tbody>
</table>

* Mann-Whitney U Test; for 3 or more categories: Kruskal-Wallis H test.
§ Positive alcohol consumption: ≥1 gram/day
### Table 3. Non-HDL-C behavior according to clinical and anthropometric characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Non-HDL cholesterol</th>
<th>( p^* )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (p25–p75)</td>
<td>( p^* )</td>
</tr>
<tr>
<td><strong>BP JNC-7</strong></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Normal blood pressure</td>
<td>132 (106–158)</td>
<td></td>
</tr>
<tr>
<td>Pre-hypertension</td>
<td>146 (118–175)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>159 (130–190)</td>
<td></td>
</tr>
<tr>
<td><strong>BMI (kg/m(^2))</strong></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>( \leq 24.9 )</td>
<td>124 (98–152)</td>
<td></td>
</tr>
<tr>
<td>25–29.9</td>
<td>148 (119–180)</td>
<td></td>
</tr>
<tr>
<td>( \geq 30 )</td>
<td>155 (129–183)</td>
<td></td>
</tr>
<tr>
<td><strong>Glycemic Status(^§)</strong></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Normo-glycemic</td>
<td>137 (110–166)</td>
<td></td>
</tr>
<tr>
<td>Impaired Fasting Glucose</td>
<td>155 (129–185)</td>
<td></td>
</tr>
<tr>
<td>DM2</td>
<td>161 (132–196)</td>
<td></td>
</tr>
<tr>
<td><strong>Waist circumference(^†)</strong></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Normal</td>
<td>132 (105–161)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>154 (128–183)</td>
<td></td>
</tr>
<tr>
<td><strong>hsCRP (mg/L)</strong></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>( &lt; 0.765 )</td>
<td>140 (109–169)</td>
<td></td>
</tr>
<tr>
<td>( \geq 0.765 )</td>
<td>156 (121–187)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BMI: Body mass index; BP: Blood pressure; hsCRP: High-sensitivity C reactive protein; JNC-7: The Seventh Report of the Joint National Committee on hypertension.

\(^†\) Cutoff for Maracaibo adult population: \( \geq 98 \) cm for men and \( \geq 91 \) cm for women.

\(^§\) American Diabetes Association (ADA) blood glucose diagnostic criteria.

*Mann-Whitney U test; for 3 or more categories: Kruskal-Wallis H test.
## Table 4. Non-HDL-C tertiles according to clinical and anthropometric characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Non HDL&lt;130</th>
<th>Non HDL=130–159</th>
<th>Non HDL≥160</th>
<th>( \chi^2 ) (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BP JNC-7</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal blood pressure</td>
<td>375</td>
<td>49.9</td>
<td>226</td>
<td>39.6</td>
</tr>
<tr>
<td>Pre-hypertension</td>
<td>262</td>
<td>34.8</td>
<td>225</td>
<td>39.4</td>
</tr>
<tr>
<td>Hypertension</td>
<td>115</td>
<td>15.3</td>
<td>120</td>
<td>21.0</td>
</tr>
<tr>
<td><strong>BMI (kg/m(^2))</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤24.9</td>
<td>343</td>
<td>45.6</td>
<td>159</td>
<td>27.8</td>
</tr>
<tr>
<td>25–29.9</td>
<td>237</td>
<td>31.5</td>
<td>201</td>
<td>35.2</td>
</tr>
<tr>
<td>≥30</td>
<td>172</td>
<td>22.9</td>
<td>211</td>
<td>37.0</td>
</tr>
<tr>
<td><strong>Glycemic Status(^\text{§})</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normo-glycemic</td>
<td>609</td>
<td>81.0</td>
<td>408</td>
<td>71.5</td>
</tr>
<tr>
<td>Impaired Fasting Glucose</td>
<td>102</td>
<td>13.6</td>
<td>116</td>
<td>20.3</td>
</tr>
<tr>
<td>DM2</td>
<td>41</td>
<td>5.5</td>
<td>47</td>
<td>8.2</td>
</tr>
<tr>
<td><strong>Waist circumference(^\text{†})</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>493</td>
<td>65.6</td>
<td>276</td>
<td>48.3</td>
</tr>
<tr>
<td>High</td>
<td>259</td>
<td>34.4</td>
<td>295</td>
<td>51.7</td>
</tr>
<tr>
<td><strong>hsCRP (mg/L)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.765</td>
<td>416</td>
<td>80.9</td>
<td>293</td>
<td>78.8</td>
</tr>
<tr>
<td>≥0.765</td>
<td>98</td>
<td>19.1</td>
<td>79</td>
<td>21.2</td>
</tr>
</tbody>
</table>

Abbreviations: BMI: Body mass index; BP: Blood pressure; hsCRP: High-sensitivity C reactive proteína; JNC-7: The Seventh Report of the Joint National Committee on hypertension.

\(^{\text{†}}\) Cutoff for Maracaibo adult population: ≥98 cm for men and ≥91 cm for women).

\(^{\text{§}}\) American Diabetes Association (ADA) blood glucose diagnostic criteria.

---

**Figure 1.** Non-HDL-C levels according to Risk Factor Clustering (MRFA). Kruskal-Wallis H Test: \( p<0.001 \).
Table 5. Logistic regression model for multiple risk factor aggregation.

<table>
<thead>
<tr>
<th>Dependent variable: MRFA (≥2 factors)</th>
<th>Odds Ratio. crude (CI 95%)</th>
<th>p&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Odds Ratio. adjusted&lt;sup&gt;c&lt;/sup&gt; (CI 95%)</th>
<th>p&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100</td>
<td>1.00</td>
<td>-</td>
<td>1.00</td>
<td>-</td>
</tr>
<tr>
<td>100–129</td>
<td>1.66 (1.33–2.08)</td>
<td>&lt;0.001</td>
<td>0.75 (0.48–1.18)</td>
<td>0.215</td>
</tr>
<tr>
<td>≥130</td>
<td>2.47 (1.99–3.08)</td>
<td>&lt;0.001</td>
<td>0.42 (0.23–0.95)</td>
<td>0.035</td>
</tr>
<tr>
<td>Colesterol Non-HDL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;130</td>
<td>1.00</td>
<td>-</td>
<td>1.00</td>
<td>-</td>
</tr>
<tr>
<td>130–159</td>
<td>2.08 (1.66–2.60)</td>
<td>&lt;0.001</td>
<td>2.59 (1.62–4.13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥160</td>
<td>3.65 (2.94–4.53)</td>
<td>&lt;0.001</td>
<td>3.75 (2.04–6.91)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<sup>a</sup> CI: Confidence Interval at 95%.
<sup>b</sup> Significance level
<sup>c</sup> Model 1 Adjusted by: sex, age groups, ethnicity, social-economic status, educative status, marital status, working status, smoking habits, alcohol consumption, physical activity in leisure time dominion, hsCRP, LDL-c and Non-HDL-c.

Discussion

For nearly 50 years, incredible efforts have been made to identify specific and prevalent ASCVD risk factors, planning and application of primary and secondary prevention strategies, evaluation of population genetics and overall ethnicity genetic risks, and modification due to epigenetics. These risk factors have been of various natures, from anthropometric measurements, such as BMI and waist circumference, lifestyle patterns, to blood lipids sub-fractions, such as LDL-c and HDL-c. In regards to the focus of the present study, lipid profiles and novel lipid fractions and their association with ASCVD have been the main focus of grand scale epidemiological, clinical, and pharmacological investigation.

In spite of all the efforts, data has been accumulating that suggests that focusing on one lipid fraction, namely LDL-c, may not be the appropriate approach, due to recently described atherogenic particles, like IDL, Apo B, and non-HDL-c. The concept of cardiovascular residual risk factor has been intimately associated with cardiovascular disease reduction, being twice as effective as LDL-c<sup>44</sup>. In fact, Helgadottir et al.<sup>35</sup> reported that genetic risk scores using non-HDL-c strongly associates with coronary artery disease, and this genetic risk was considerably lower than that offered by LDL-c. It is no coincidence that non-HDL-c has been shown to correlate with coronary artery disease progression, cardiovascular morbidity, and mortality.<sup>44,45</sup>

The present results show that higher non-HDL-c levels were associated with higher risk of multiple risk factors for ASCVD. These results are similar to those reported by Kumar et al.<sup>37</sup> where non-HDL-c had a better predictive value than LDL-c for atherosclerosis among those with TGs >150 mg/dl<sup>37</sup>. This study excluded patients with increased TGs >400 mg/dl; therefore, one cannot assume this association is also seen in this group. Moreover, Arsenault et al.<sup>38</sup> followed over 21 thousand subjects without diabetes or previous coronary heart disease (CHD), demonstrating that high non-HDL-c is associated with increased CHD.

Following the recommendation of the Strong Heart Study<sup>39</sup>, the recent 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk proposed a goal of <100 mg/dl for non-HDL-c in diabetic patients<sup>40</sup>. As expected, subjects with diabetes in our population have higher non-HDL-c, which is a recognized risk factor in diabetic subjects at risk for ASCVD<sup>41</sup>. Interestingly, Apo B and non-HDL-c are better predictors of diabetes development than glycated hemoglobin<sup>42</sup>. In line with this notion, the present results also show that non-HDL-c is associated with higher levels of hs-CRP (systemic inflammation), hypertension, and central obesity. We previously described our population as having a high prevalence of obesity and overweight, managing a staggering 65.7%<sup>43</sup>. Thus, the overlapping of risk factors and metabolic syndrome/type 2 diabetes development is imminent and borderline epidemic.

Lastly, Hispanic population seems to be at higher risk for LDL-particle numbers and non-HDL-c discordance<sup>44</sup>.
Kilgore et al. reported that subjects with high non-HDL-c and normal LDL-c were likely to be Hispanic males with metabolic syndrome and other cardiovascular risks. Likewise, using the database from The Hispanic Community Health Study/Study of Latinos, Rodriguez et al. reported that almost two thirds of Latinos have a form of dyslipidemia, with South Americans having high non-HDL-c and high LDL-c. Therefore, ethnicity is of high importance when evaluating clinical risk for ASCVD, including blood lipid profiles and sedentary lifestyles in these groups.

To summarize, this investigation in Hispanic population shows that non-HDL-c is associated with multiple risk aggregation for ASCVD, being associated with hypertension, central obesity and low grade inflammation. The question that arises is: Should non–HDL-c replace LDL-C as the main target of therapy? The fact that non–HDL-c is a better risk predictor, can be performed in a non-fasting state, and can be easily calculated by extracting HDL-c from total cholesterol without using any other laboratory assay makes it the most advantageous parameter for prediction of ASCVD even in subjects with TAG <200 mg/dl.

**Data availability**

Dataset 1: MMSPS non-HDL and atherosclerotic cardiovascular disease risk factors raw data. DOI, 10.5256/f1000research.13005. d195980

**Competing interests**

No competing interests were disclosed.

**Grant information**

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The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Chandrakala Aluganti Narasimhulu
Univeristy of Central Florida, Orlando, Florida, USA

The present study “Non-HDL cholesterol is better than LDL-c at predicting atherosclerotic cardiovascular disease risk factors clustering, even in subjects with near-to-normal triglycerides: A report from a Venezuelan population” by Bermúdez et al., is interesting however, the authors must address the following key points:

- In results, (Table 2) the non-HDL cholesterol levels were represented based on age groups. In addition to this if the authors provide the analysis for men and women separately which will be more accurate.
- Table 3 to 5: if the analysis done for both men and women separately that provides more insights for both clinicians and researchers.
- Authors are suggested to comment/discuss briefly the hormonal influence in disease progression in both genders.

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?
Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Cardiovascular disease

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.

Chau-Chung Wu
Graduate Institute of Medical Education and Bioethics, National Taiwan University College of Medicine, Taipei, Taiwan

The study showed elevated non-HDL-c was associated with conglomeration of multiple risk factors for ASCVD. The result is predictable and not novel. It has been shown in many previous publications. However, one major concern about the methodology: Were the blood pressure and sugar measured before any treatment or just on treatment? The authors should clarify it, because it may change the risk calculation in some patients, esp. for those already with hypertension or diabetes mellitus from the beginning of the study.

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?
Partly

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.
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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