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Research Article

Prevalence, Lipid Abnormalities Combinations and Risk Factors Associated with Low HDL-C Levels in Maracaibo City, Venezuela

Valmore Bermúdez*[1],Juan Salazar[1],Joselyn Rojas[1],María Sofía Martínez[1],Luis Bello[1],Roberto Añez[1],Robys González[1],Carmen Chávez[1],Vanessa Apruzzese[1],Wheeler Torres[1],José Carlos Mejía[1],Edgar Miquilena[1],Maricarmen Chacín[1],Clímaco Cano Ponce[1],Manuel Velasco[2],José López-Miranda[3]

[1]*Endocrine-Metabolic Research Center, "Dr. Félix Gómez," School of Medicine, University of Zulia, Maracaibo, Venezuela*

[2]*Clinical Pharmacologic Unit. Vargas Medical School, Central University of Venezuela. Caracas, Venezuela*

[3]*Lipid and Atherosclerosis Unit, Department of Medicine. IMIBIC/Reina Sofia University Hospital/University of Córdoba, and CIBER Fisiopatología, Obesidad y Nutrición (CIBEROBN), Instituto de Salud Carlos III, Spain*

**Corresponding author: Dr. Valmore Bermúdez, Endocrine and Metabolic Diseases Research Center, University of Zulia, Maracaibo, Venezuela, Email: valmore@gmail.com*

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Abstract

The purpose of this study was to analyze the epidemiologic behavior of HDL-C and the factors associated with Low HDL-C within the Maracaibo city Metabolic Syndrome Prevalence Study (MMSPS). A total of 2,230 individuals from both sexes were enrolled in the MMSPS. Low levels of HDL-C were defined according to ATP-III criteria. Qualitative variables were expressed as absolute and relative frequencies, using chi^2 test for association assessment. A logistic regression model was built to evaluate the main risk factors associated with Low levels of HDL-C. Low Level HDL-C (isolated and combined) was 57.8% (n=1,288), 751 women and 537 men. Prevalence of Isolated Low HDL-C was 17.6%, while Low HDL-C + High LDL-C was 19.6%, Mixed Dyslipidemia was 16.2%, and Low HDL-C + Hypertriacylglyceridemia was 4.3%. Higher risk for Low HDL-C was observed in Men with obesity (OR 1.93; IC95%1.22-3.04) and Hypertriacylglyceridemia (OR 2.19, IC95%1.68-3.11), and Women of Amerindian ethnicity (OR: 2.78, IC95%1.26-6.13), currently unemployed (OR 1.60, IC95%1.19-2.15) and Hypertriacylglyceridemic (OR: 3.18, IC95%2.14-4.73); a slightly lower risk was observed in women with low alcohol intake (OR 0.54, IC95%0.29-1.00). There is a high prevalence of Low HDL-C in our study, raising the possibility that HDL-C cutpoints may not be suited for our population. This type of dyslipidemia was associated with obesity, ethnic group, employment, hypertriacylglyceridemia and alcohol consumption.

Keywords: High Density Lipoprotein; Dyslipidemia; Isolated Low HDL-C; Coronary Artery Disease; Metabolic Syndrome; Obesity; Alcohol Consumption

Introduction

According to World Health Organization (WHO), Cardiovascular Disease (CVD) is the main cause of death in the adult population worldwide [1], with a tendency to lower in high income countries around the world [2]. According to the latest heart disease and stroke, which uses the NHANES database [3], 31.8% (34.6 million) of men and 12.3% (14.1 million) of women with CVD have Low HDL-C. Worldwide results from prospective and case-control studies have demonstrated that low serum levels of HDL-C are considered a major independent cardiovascular risk factor, among them the Framingham Study [4], the Prospective Cardiovascular Münster Study (PROCAM) [5], and The InterHeart Study [6]. In the PREV-ICTUS study, Low HDL-C was independently associated with CVD with OR 1.46 (IC95% 1.22-1.74, p<0.001) in both genders [7]. Meanwhile, in the RIHMA study, hypertensive women were at higher risk for silent target organ damage when HDL-C were low with OR 1.31 (IC95% 1.15-1.49, p<0.001) [8]. This lipid disorder has been also associated with higher risk for Alzheimer´s disease (HR: 0.4, IC95% 0.2-0.9, p=0.03) [9], longevity (HR, 0.72; 95% CI, 0.55 to 0.94) [10] and cancer (pooled RR: 1.15, IC95% 1.01-1.32) [11].

Venezuela doesn´t escape this scenario, with 21.36% cardiovascular-related deaths by 2011 using local information [12]; however the latest Noncommunicable Diseases Country Profile [13] published by the WHO, reported that by 2011 31% of annual mortality was associated with CVD, followed by 21% injury-related deaths. In the Zulia state, similar indicators have been reported, where 23.4% of overall deaths were attributed to CVD in 2008 [14].

Low HDL-C concentration as a risk factor has been evaluated for different settings and diseases. High Density Lipoprotein concentration varies according to the population analyzed. Previous research has shown a high prevalence of Low HDL-C Syndrome (HDL-C <40 mg/dL) in Hispanic populations compared to other ethnic groups (5,6), which begs the question of a unique genetic profile interacting with environmental factors which renders a specific phenotype for Latinos (15). Moreover, the analysis of cardiometabolic risk is still incomplete, and not all regions of the world are represented in the current risk factor data. Contrary to European populations, Latin American subjects reside within in a very heterogeneous geographical, sociocultural and genetic context, which makes risk discerning quite more complex and the necessity of local cross-sectional and prospective studies yet more imperative [4,6,15].

In light of all this information, the purpose of this study was to analyze the epidemiologic behavior of HDL-C in the in the adults enrolled in the Maracaibo City Metabolic Syndrome Prevalence Study (MMSPS), with specific description of its tendencies within age groups and ethnicities, current state according to latest classification criteria, and finally, assessment of coronary risk in our population according to resulting levels of HDL-C.

Materials and Methods

Ethical Considerations

All participants signed a written consent before being interrogated and physically examined. The study was approved by the Ethics Committee of the Endocrine and Metabolic Diseases Research Center "Dr. Félix Gómez".

Subject Evaluation

The Maracaibo City Metabolic Syndrome Prevalence Study is a cross-sectional study with a randomized multietapic sampling, whose methodology has been published elsewhere [16]. Sociodemographic (ethnicity, educational and socioeconomic status, work condition) and psychobiological habits (smoking and drinking habits) were obtained through a medical history chart. Smoking habits were evaluated according to the following: Current smokers, Non-smokers, and ex-smokers (at least 1 year of having quit the habit). Alcohol consumption was divided in quartiles according to the grams of alcohol consumed per day. Physical activity (PA) levels were estimated using the long version of the International Physical Activity Questionnaire (IPAQ) [17]. Once the data was obtained in the leisure time sphere, it was divided in two big groups, individuals with MET's=0 (Inactive) and those with METs >0. Afterwards, this last group was divided into quintiles, obtaining the following classification: (Q1 or very low: [Male: <296,999; Female: <230,999], Q2 or Low: [Male: 297,000-791,999; Female: 231,000-445,499], Q3 or Moderate: [Male: 792,000-1532,399; Female: 445,500-742,499], Q4 or High: [Male: 1532,400-2879,999; Female: 742,500-1798,499], Q5 or Very High: [Male: >2879,000; Female: 1798,500]). Blood pressure was classified using The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) [18]. The anthropometric evaluation was carried out using Body Mass Index (BMI) as quantification of adiposity with the formula [weight/height^2], classifying the subjects according to WHO standards [19]. Waist circumference was determined employing a measure tape in accordance to the anatomical landmarks proposed by the National Institutes of Health protocol [20], classifying abdominal obesity as Men ≥90 cm and Women ≥80 cm [21]. Using the Framingham-Wilson equation properly calibrated for our population [22], the coronary risk at 10 years was calculated for this subsample (n=1379) according to HDL-C levels.

Laboratory Analysis

Fasting serum levels of glucose, total cholesterol, TAG, and HDL-C were determined employing commercial enzymat-

ic-colorimetric kits and specialized computerized equipment (Human Gesellschaft für Biochemica und Diagnostica mbH, Germany). LDL-C levels were calculated through Friedewald's formula [23]. If TAG values were beyond 400 mg/dL, LDL was calculated using lipoprotein electrophoresis, and measured by optical densitometry (BioRad® GS 400, USA). Fasting insulin levels were assessed by double antibody ELISA method (DRG International Inc. New Jersey, USA). Insulin resistance (IR) was calculated using the HOMA-Calculator v2.2.2 software supplied by the Oxford Centre for Diabetes Endocrinology and Metabolism available: http://www.dtu.ox.ac.uk/homacalculator/index.php; HOMA2-IR cut-off point used was 2.00 as previously established in our population [24].

Lipid Disorders

The following dislipidemia definitions were used:

- Isolated Low HDL-C: HDL-C <40 mg/dL for men and <50 mg/dL for women (IDF/NHLBI/AHA-2009 consensus [21] in absence of another lipid disorder.
- Isolated Hypertriacylglyceridemia: TAG ≥150 mg/dL in absence of another lipid disorder (ATPIII [25]).
- Isolated Hypercholesterolemia: total Cholesterol <200 mg/dL [25].
- Elevated LDL-C: >130 mg/dL [25].
- Mixed Dislipidemia: Hypercholesterolemia occurring with Hypertriacylglyceridemia and Low HDL-C [26].
- Other combinations: a) Low HDL-C + High LDL-C, b) Low HDL-C ++ Hypertriacylglyceridemia.

Statistical Analysis

Normal distribution of continuous variables was evaluated by using Kolmogorov-Smirnov (when n<500) or Geary's (when n ≥500) test, accordingly. Variables without normal distribution were logarithmically transformed, and normal distribution later corroborated. Differences between arithmetic means were assessed using Student's t-test (when two groups were compared) or ANOVA (when three or more groups were compared). Qualitative variables were expressed as absolute and relative frequencies, and evaluation of association was calculated with chi^2 test, considered significant when p<0.05. Coronary risk was expressed as median and p25-p75 due to its not normal distribution, and differences between risks percentages were obtained with Mann- Whitney U-test. A Logistic Regression model was constructed to estimate odds ratio (IC95%) for low HDL-C for each sex. In the first model, the following variables were adjusted: age groups, ethnic groups, working status, smoking habit, alcohol consumption, physical activity in leisure time, presence of Insulin Resistance, glycemic status (normoglycemic, fasting altered glucose, or type 2 diabetes), BMI and Blood Pressure classification. In the second model, abdominal obesity diagnosis was added. Finally, in a third model, hypertriglyceridemia diagnosis was included. The database analyses were performed using the statistical package for the social science (SPSS) v.19 for Windows (IBM Inc. Chicago, IL, USA), considering significant results as values p<0.05.

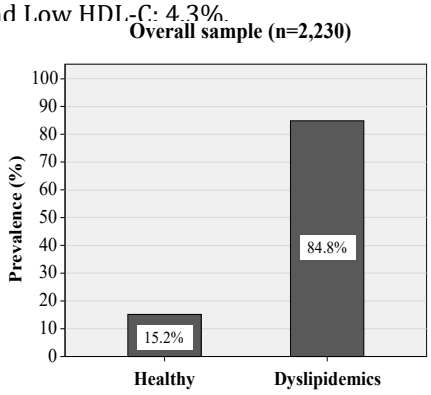
Results

General Characteristics of the Population

The MMSPS had an overall sample of 2,230 individuals of both genders, with 1,059 (47.5%) men and 1,171 (52.5%) women. Selected demographic characteristics of the population according to sex are shown in **Table 1**. Average age in the sample was 39.3±15.4 years, (40.8±15.8 years for women, and 37.7±14.9 years for men; p<0.001).

Overall Prevalence of Dyslipidemia

The results obtained in this investigation show that there were 84.8% (n=1891) of subjects with any type of dyslipidemia (**Figure 1**). Moreover, the distribution of each phenotype in general population and by gender was as follows: Other dyslipidemias (27.1%), Low HDL-C and Elevated LDL-C: 19.6%, Isolated Low HDL-C 17.6%, Mixed Dyslipidemia 16.2%, Elevated TAG and Low HDL-C: 4.3%.



	Women		Men		Total	
Phenotype	**n**	**%**	**n**	**%**	**n**	**%**
Normal Lipids	141	12.0	197	18.6	338	15.2
Isolated Low HDL-C	236	20.2	157	14.8	393	17.6
Low HDL-C + High LDL	295	25.2	143	13.5	438	19.6
Low HDL-C + High TAG	29	2.5	66	6.2	95	4.3
Mixed Dyslipidemia	190	16.2	171	16.1	361	16.2
Other dyslipidemia	280	23.9	325	30.7	605	27.1
Total	**1171**	**100**	**1059**	**100**	**2230**	**100**

Low HDL-C: Men: <40mg/dL; Women: <50mg/dL.
High LDL: ≥130 mg/dL
High Triglycerides (TAG): ≥150 mg/dL.
Other dyslipidemia include: High LDL, High TAG, Elevated LDL and TAG.

Figure1. Prevalence of Dislipidemia in the overall population and its combinations in individuals with lipid abnormalities in the Maracaibo city Metabolic Syndrome Prevalence Study - Venezuela, 2014.

Table 1. General characteristics of the population enrolled in the Maracaibo city Metabolic Syndrome Prevalence Study - Venezuela, 2014.

	Female (n=1 171)	Male(n=1 059)	All (n=2 230)
	n (%)	n (%)	n (%)
Age Groups			
< 20	100 (8.5)	80 (7.6)	180 (8.1)
20-29	249 (21.2)	332 (31.4)	581(26.1)
30-39	197 (16.8)	199 (18.8)	396 (17.8)
40-49	269 (23.0)	193 (18.2)	462 (20.7)
50-59	205 (17.5)	165 (15.5)	369 (16.5)
60-69	102 (8.7)	61 (5.8)	163 (7.3)
≥ 70	50 (4.3)	29 (2.7)	79 (3.5)
Ethnic Groups			
Mixed Groups	876 (74.7)	816 (77.1)	1692 (75.9)
Hispanic Whites	191 (16.3)	161 (15.2)	352 (15.8)
Afro-Venezuelan	30 (2.6)	36 (3.4)	66 (3.0)
Amerindians	62 (5.3)	44 (4.2)	106 (4.8)
Others	13 (1.1)	1 (0.1)	14 (0.6)
Working Status			
Employed	496 (42.3)	727 (68.7)	1223 (54.8)
Unemployed	642 (54.8)	291 (27.5)	933 (41.8)
Underemployed	34 (2.9)	40 (3.8)	74 (3.3)
Body Mass Index (BMI)			
<24.99 Kg/m^2	420 (35.8)	275 (26.0)	695 (31.2)
25 – 29.9 Kg/m^2	371 (31.7)	415 (39.2)	786 (35.2)
≥ 30 Kg/m^2	381 (32.5)	368 (34.8)	749 (33.6)
Waist Circumference*			
Normal	246 (21.0)	309 (29.2)	555 (24.9)
Elevated	926 (79.0)	749 (70.8)	1675 (75.1)
Insulin resistance**			
Absent	563 (53.3)	520 (53.6)	1083 (53.5)
Present	493 (46.7)	450 (46.4)	943 (46.5)
Total	1171 (52.5)	1059 (47.5)	2230 (100)

* Elevated Waist Circumference (Men: ≥90cm; Women: ≥80cm).

** Calculated using the HOMA-IR formula. Cut-off level ≥2.

Prevalence of Low HDL-C

When distributing HDL-C according to percentiles (**Table 2**), total median HDL-C was 43.0 (36.0-50.0), while women rendered a median of 46.0 (39.0-53.0) and men 39.0 (34.0-46.0). Prevalence of Low Level HDL-C (isolated or combined)

was 57.8% (n=1,288 from the overall sample of 2230 individuals), 64.1% (n=751) in women and 50.7% (n=537) in men; **Figure 2**. Mean HDL-C obtained was 46.9±11.9 mg/dL and 40.9±11.4 mg/dL for women and men, respectively. **Table 3** shows the behavior of HDL-C levels according to age groups in the general population and gender, finding higher levels in the 20-59 yrs group in both men and women. Significant differences are observed in HDL-C levels according to sex in every age group except in the ≥70 yrs group.

Table 2. Levels of HDL-C according to percentiles in the Maracaibo city Metabolic Syndrome Prevalence Study - Venezuela, 2014.

	HDL-C (mg/dL)				
	p05th	p25th	p50th	p75th	p95th
Female	30.00	39.00	46.00	53.00	67.00
Male	26.00	34.00	39.00	46.00	61.00
All	28.00	36.00	43.00	50.00	65.00

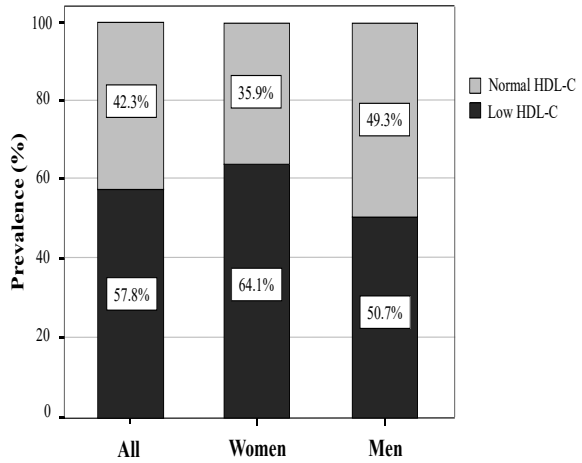


Figure 2. Prevalence of Normal and Low HDL-C levels according to sex in the population enrolled in the Maracaibo city Metabolic Syndrome Prevalence Study - Venezuela, 2014.

Table 3. HDL-C levels according to age group and sex in the population enrolled in the Maracaibo city Metabolic Syndrome Prevalence Study - Venezuela, 2014.

	HDL-C (mg/dL)								
	Women			Men			Total		
Age groups (years)	Mean	SD	p*	Mean	SD	p*	Mean	SD	p*
<20	47.9	11.4	0.01	41.8	9.7	<0.0001	45.2	11.1	<0.0001
20-29	49.4	11.8		43.9	14.0		46.2	13.4	
30-39	46.1	10.7		39.7	10.4		42.9	11.0	
40-49	46.3	12.3		38.1	9.2		42.9	11.8	
50-59	45.6	12.1		40.9	9.7		43.5	11.3	
60-69	46.3	11.2		36.6	7.0		42.6	10.9	
≥70	46.2	14.6		41.7	10.1		44.5	13.3	
Total	**46.9**	**11.9**		**40.9**	**11.4**		**44.1**	**12.0**	

SD=Standard Desviation
* One-way ANOVA
Post-Hoc Tukey Analysis:
Women: 20-29 vs 30-39: p=0.06; 20-29 vs 40-49: p=0.05; 20-29 vs 50-59: p=0.01
Men: 20-29 vs 30-39: p<0.001; 20-29 vs 40-49: p<0.0001; 20-29 vs 60-69: p<0.0001
Total: 20-29 vs 30-39: p<0.001; 20-29 vs 40-49: p<0.0001; 20-29 vs 50-59: p<0.01; 20-29 vs 60-69: p<0.01

HDL-C Levels According to Sex and Ethnic Group

HDL-C levels according sex and ethnicity are presented in **Table 4**. Overall Amerindians obtained the lowest levels of HDL-C when comparing with other ethnic groups (p=0.03). Amerindians women had the lowest levels of HDL-C with 41.7±8.9 mg/dL, having significant difference with Mixed Race women (46.8±11.6 mg/dL; p=0.01); Hispanic Whites women (48.9±12.1 mg/dL; p<0.01) and Afro-Venezuelan women (49.8±12.1 mg/dL; p<0.02). No differences were observed between arithmetic mean within the men´s groups. When evaluating HDL-C levels, according to presence or absence of Low HDL-C levels, no significant difference were observed between ethnic groups.

Table 4. HDL levels according to ethnic groups in the population enrolled in the Maracaibo city Metabolic Syndrome Prevalence Study - Venezuela, 2014.

		Mixed race	Hispanic whites	Afro-Venezuelan	Amerindian	Others	p*
Normal HDL (mg/dL)	Female	58.8±9.1	60.6±10.8	59.1±8.4	55.7±5.9	64.7±11.7	0.34
	Male	49.3±10.9	48.6±9.5	50.7±10.2	46.8±7.9	-	0.57
Low HDL (mg/dL)	Female	40.2±6.3	39.7±6.5	40.5±6.9	39.1±6.5	40.3±6.7	0.76
	Male	33.1±4.5	32.9±4.2	31.2±5.5	31.7±5.0	38.0	0.21
Total	Female	46.8±11.6	48.9±13.5	49.8±12.1	41.7±8.9	45.9±13.1	<0.01
	Male	41.0±11.6	40.7±10.7	42.0±12.9	39.3±10.1	38.0	0.87 0.03
	All	**44.0±11.9**	**45.2±12.9**	**45.6±13.0**	**40.7±9.4**	**45.4±12.7**	

* One-way ANOVA

Low HDL-C and Coronary Risk Score

Applying the calibrated Framingham-Wilson equation, coronary risks was attested between those with Low HDL-C and those with normal levels of this particle (**Table 5**). As expected, women with Low HDL-C obtained higher coronary risk results (1.71 vs. 3.40; p<0.0001), pattern that was also observed in men (3.44 vs.4.73; p<0.0001).

Table 5. Coronary risk according to a calibrated Framingham formula and HDL-C levels in the population enrolled in the Maracaibo city Metabolic Syndrome Prevalence Study - Venezuela, 2014.

	Coronary Risk at 10 years (%)								
	Normal HDL-C				Low HDL-C				
	n	p25th	Median	p75th	n	p25th	Median	p75th	p*
Female	258	0,72	1,71	3,17	513	1,29	3,40	6,48	<0.001
Male	266	1,97	3,44	5,95	342	2,75	4,73	8,66	<0.001

* U-Mann Whitney Test

Risk factors for Low HDL-C

The most frequent risk factors associated with Low HDL-C in both women and men are shown in **Tables 6** and **7**, respectively. Amerindian women obtained the highest risk for Low HDL-C (OR: 2.78, IC95% 1.26-6.13; p<0.01), while Hispanic

Table 6. Logistic regression for the factors associated with low HDL-C in the Female population enrolled in the Maracaibo city Metabolic Syndrome Prevalence Study - Venezuela, 2014.

	Model 1*		Model 2**		Model 3***			
	Odds Ratio (IC 95%[a])	p[b]	Adjusted Odds Ratio (IC 95%[a])	p[b]	Adjusted Odds Ratio (IC 95%[a])	p[b]	Adjusted Odds Ratio (IC 95%[a])	p[b]
Working Status								
Employed	1.00	-	1.00	-	1.00	-	1.00	-
Unemployed	1.48 (1.16 - 1.89)	< 0.01	1.54 (1.16 - 2.06)	< 0.01	1.59 (1.19 - 2.12)	< 0.01	1.60 (1.19 - 2.15)	< 0.01
Underemployed	2.29 (1.02 - 5.16)	0.05	2.11 (0.85 - 5.22)	0.11	2.02 (0.82 - 5.02)	0.13	1.99 (0.78 - 5.03)	0.15
Ethnic Groups								
Mixed	1.00	-	1.00	-	1.00	-	1.00	-
Hispanic Whites	0.69 (0.50 - 0.95)	0.02	0.71 (0.50 - 1.01)	0.06	0.70 (0.49 - 0.99)	0.05	0.61 (0.40 - 0.88)	< 0.01
Afrovenezuelans	0.54 (0.26 - 1.12)	0.10	0.52 (0.23 - 1.17)	0.11	0.50 (0.22 - 1.11)	0.09	0.46 (0.20 - 1.07)	0.07
Ameirndians	2.82 (1.41 - 5.62)	< 0.01	2.62 (1.20 - 5.70)	0.02	2.75 (1.25 - 6.03)	0.01	2.78 (1.26 - 6.13)	< 0.01
Others	1.81 (0.49 - 6.62)	0.37	2.16 (0.45 - 10.40)	0.34	2.12 (0.44 - 10.28)	0.35	2.52 (0.51 - 12.31)	0.15
Alcohol consumption (gr/day)								
No consumption	1.00	-	1.00	-	1.00	-	1.00	-
< 6.04	0.71 (0.40 - 1.23)	0.22	0.81 (0.44 - 1.51)	0.51	0.85 (0.46 - 1.58)	0.60	0.86 (0.46 - 1.61)	0.64
6.04 - 20.1	0.52 (0.30 - 0.91)	0.02	0.54 (0.29 - 1.00)	0.05	0.53 (0.28 - 0.99)	0.05	0.54 (0.28 - 1.02)	0.06
20.2 - 40.5	1.37 (0.74 - 2.52)	0.32	1.35 (0.67 - 2.73)	0.40	1.25 (0.62 - 2.52)	0.54	1.26 (0.61 - 2.58)	0.53
> 40.5	0.97 (0.55 - 1.71)	0.92	1.05 (0.54 - 1.87)	0.99	0.98 (0.52 - 1.82)	0.94	1.04 (0.55 - 1.95)	0.91
Insulin resistance[c]								
Absent	1.00	-	1.00	-	1.00	-	1.00	-
Present	1.63 (1.26 - 2.10)	< 0.01	1.37 (1.03 - 1.83)	0.03	1.37 (1.02 - 1.83)	0.04	1.26 (0.94 - 1.70)	0.12
Body Mass Index (Kg/m^2)								
≤ 24.9	1.00	-	1.00	-	1.00	-	1.00	-
25 – 29.9	1.25 (0.94 - 1.66)	0.13	1.28 (0.91 - 1.78)	0.15	1.05 (0.73 - 1.51)	0.79	1.03 (0.71 - 1.49)	0.88
≥ 30	2.16 (1.60 - 2.91)	< 0.01	1.67 (1.14 - 2.43)	< 0.01	1.34 (0.88 - 2.02)	0.17	1.30 (0.86 - 1.99)	0.22
Elevated Waist Circumference								
Absent	1.00	-	-	-	1.00	-	1.00	-
Present	1.99 (1.49 - 2.64)	< 0.01	-	-	1.76 (1.17 - 2.62)	< 0.01	1.71 (1.14 - 2.57)	0.01
Hypertriglyceridemia								
Absent	1.00	-	-	-	-	-	1.00	-
Present	3.04 (2.18 - 4.25)	< 0.01	-	-	-	-	3.18 (2.14 - 4.73)	< 0.01

a Confidence Interval (95%); **b** Level of Significance ; **c** HOMA2IR ≥2

*** Model 1**: Adjusted by age groups, ethnic groups, working condition, smoking, alcohol consumption, leisure time physical activity, insulin resistance, glycemic status, BMI and JNC-7 classification.

**** Model 2**: Adjusted by previous and elevated waist circumference (Women: ≥80cm).

***** Model 3** : Adjusted by previous and hypertriglyceridemia (TAG≥150 mg/dL).

White women seem to have lower risk with OR 0.61 (IC95% 0.40-0.88; p<0.01). Other associated parameters in women were Hypertriacylglyceridemia (OR: 3.18, IC95% 2.14-4.73; p<0.01), abdominal obesity (OR: 1.71, IC95% 1.14-2.57; p=0.01), Unemployment (OR: 1.60, IC95% 1.19-2.15; p<0.01) and Insulin Resistance (OR: 1.37, IC95% 1.02-1.83; p=0.04).

However, women with low alcohol consumption (6.04-20.1 gram/day) were slightly associated with lower risk for this lipid abnormality, with OR 0.54 (IC95% 0.29-1.00; p=0.05). On the other hand, men with hypertriglyceridemia (OR 2.19, IC95% 1.68-3.11; p<0.01), abdominal obesity (OR 1.93, IC95% 1.22-3.04; p<0.01) and Insulin Resistance (OR: 1.39, IC95% 1.04-1.88; p=0.03) are at higher risk for Low HDL-C.

Table 7. Logistic regression for the factors associated with low HDL-C in the Male population enrolled in the Maracaibo city Metabolic Syndrome Prevalence Study - Venezuela, 2014.

	Model 1*		Model 2**		Model 3***			
	Odds Ratio (IC 95%[a])	*p*[b]	Adjusted Odds Ratio (IC 95%[a])	*p*[b]	Adjusted Odds Ratio (IC 95%[a])	*p*[b]	Adjust Odds Ratio (IC 95%[a])	*p*[b]
Age Groups (years)								
<20	1.00	-	1.00	-	1.00	-	1.00	-
20-29	1.08 (0.66 - 1.77)	0.77	0.87 (0.49 - 1.56)	0.64	0.79 (0.44 - 1.44)	0.45	0.76 (0.42 - 1.37)	0.36
30-39	1.83 (1.08 - 3.10)	0.02	1.25 (0.66 - 2.40)	0.49	1.07 (0.55 - 2.07)	0.84	0.92 (0.47 - 1.81)	0.81
40-49	2.01 (1.19 - 3.42)	0.01	1.28 (0.66 - 2.49)	0.46	1.10 (0.56 - 2.16)	0.78	0.91 (0.46 - 1.82)	0.80
50-59	1.32 (0.77 - 2.27)	0.31	0.85 (0.43 - 1.67)	0.63	0.69 (0.34 - 1.37)	0.28	0.58 (0.29 - 1.18)	0.13
60-69	3.40 (1.68 - 6.91)	< 0.01	2.23 (1.00 - 5.05)	0.05	1.75 (0.76 - 4.02)	0.19	1.62 (0.70 - 3.77)	0.26
≥70	1.16 (0.49 - 2.73)	0.74	0.85 (0.32 - 2.21)	0.73	0.67 (0.25 - 1.77)	0.42	0.61 (0.23 - 1.64)	0.33
Insulin resistance[c]								
Absent	1.00	-	1.00	-	1.00	-	1.00	-
Present	1.93 (1.49 - 2.49)	< 0.01	|	0.03	1.34 (0.99 - 1.81)	0.06	1.22 (0.90 - 1.66)	0.21
Body Mass Index (Kg/m^2)								
≤ 24.9	1.00	-	1.00	-	1.00	-	1.00	-
25 – 29.9	1.95 (1.42 - 2.67)	< 0.01	1.74 (1.21 - 2.48)	< 0.01	1.17 (0.75 - 1.81)	0.50	1.08 (0.69 - 1.69)	0.73
≥ 30	3.04 (2.19 - 4.20)	< 0.01	2.31 (1.55 - 3.45)	< 0.01	1.41 (0.84 - 2.34)	0.19	1.30 (0.78 - 2.19)	0.32
Elevated Waist Circumference								
Absent	1.00	-	-	-	1.00	-	1.00	-
Present	2.69 (2.04 - 3.54)	< 0.01	-	-	2.03 (1.30 - 3.19)	< 0.01	1.93 (1.22 - 3.04)	< 0.01
Hypertriglyceridemia								
Absent	1.00	-	-	-	-	-	1.00	-
Present	2.97 (2.27 - 3.89)	< 0.01	-	-	-	-	2.29 (1.68 - 3.11)	< 0.01

a Confidence Interval (95%); **b** Level of Significance ; **c** HOMA2IR ≥2

*** Model 1**: Adjusted by age groups, ethnic groups, working condition, smoking, alcohol consumption, leisure time physical activity, insulin resistance glycemic status, BMI and JNC-7 classification.

**** Model 2**: Adjusted by previous and elevated waist circumference (Men: ≥90cm).

***** Model 3** : Adjusted by previous and hypertriglyceridemia (TAG≥150 mg/dL).

Discussion

Low HDL-C Syndrome is one of the most prevalent dyslipidemia around the world [4-6,15], associated not only with CVD [7,8] but also with an ample array of diseases such as Alzheimer´s disease [9] and cancer [11]. Within the broad umbrella of risk factors for CVD, this particular phenomenon alongside elevated levels of Low Density Lipoprotein (LDL) constitutes one of the fundamental building-blocks of the atheromatous plaque [27]. The elevated prevalence of low HDL-C is a trait observed in several locations, particularly in Latin America and South Asia [28]. Taking into consideration CVD-related mortality observed in Venezuela and in the Zulia state, the evaluation of the epidemiological factors and Low HDL-C levels is mandatory.

According to the NHANES database, 21.8% of the individuals have Low HDL-C [3], being higher in Mexican-American men (34.2%) and women (15.1%) compared to other ethnicities [3]. In Mexico, Aguilar-Salinas et al. [29] reported a prevalence of Low HDL-C of 46.2% for men and 28.7% for women, while countries such as Korea are burdened with higher prevalences, with 45.2% of men and 63.9% from their KNHANES data (30). In a pan-European survey, Bruckert et al. [30] observed a prevalence of Low HDL-C of 33% in men and 40% in women even in spite of treatment, and moreover, prevalence of very low HDL-C (<35 mg/dL) was seen in 14% of dyslipidemic subjects [31]. Our results show an overall prevalence of 57.8%, which seems to be higher than results obtained from United States, México and Korea, with higher results in women than in men.

In regards to Isolated Low HDL-C phenotype prevalence, Aguilar-Salinas et al. [29] published that Isolated Low HDL-C was seen in 18.6% of the sample, 22% in men and 16% in women. Higher results have been reported, such as Sharifi et al. [32] who published a prevalence of 13% of Isolated Low HDL-C (<35 mg/dL) and 63% with HDL-C below 40 mg/dL. Finally, in a meta-analysis from Asian-Pacific region studies [33], isolated Low HDL-C was observed in 22.4% of Asians, conferring a CVD risk of 1.67 (IC95% 1.27-2.19). Our findings suggest that Isolated Low HDL-C is lower in our population (17.6%) than in other studies; however, such differences can be explained due to methodological aspects, nutritional characteristics and different genetic backgrounds which can influence the results.

Several factors have been associated with Low HDL-C. In the case of obesity, several mechanisms have been proposed to correlate this metabolic disorder with HDL-C, including increased lipoprotein catabolism and decrease synthesis of Apo A-1 [34]. Obesity defined by elevated BMI was been associated with Isolated Low HDL-C in men and women in our study; however the regression model showed that elevated abdominal circumference demonstrated the highest risk in presenting with this dyslipidemia, results that are in accordance to what Wang and Peng [35] suggested, that adipokines are involved in HDL-C metabolism. Indeed, we have previously discussed the role of the sick adipocyte in the metabolic disorders observed in those with metabolically obese blood chemistry profiles (36), where adipose tissue hypoxia and subsequent invasion with inflammatory macrophages induces secretion of inflammation mediators such as TNF-a, IL6, resistin and IL-1b that modify lipid partition and cholesterol reverse pathways [36].

Moreover, women with insulin resistance exhibit higher risk for low HDL-C levels, but such influence is lost when the model is adjusted by TAG, suggesting that in women the relationship between dyslipidemia and insulin resistance depends in the development of hypertriacylglyceridemia. Taking these findings into account, future studies need to focus the importance of TAG/HDL ratio as a metabolic disorder predictor especially in women, as was reported by the MONET study [37], where this ratio was found to be a good predictor for HOMA and glucose disposal in overweight and obese postmenopausal women.

Sociodemographic and psychobiological factors also play an important role in Low HDL-C Syndrome, where employment status seems to protect individuals against this disturbance in women. However, subjects with low socioeconomic status are usually more insulin resistant, hyperglycemic and hypertensive, which puts them at risk as well [38,39]. With regards of alcohol several considerations have to be made. There is epidemiological confirmation that moderate ingestion is associated with elevated levels of HDL-C related to enhanced cholesterol efflux by ABCA1 [40]; even more, moderate alcohol intake has been associated with increased HDL-C levels in postmenopausal women [41], bringing into question whether alcohol is cardioprotective [42], and if so, what are the cut-off levels of ingestion before the damaging effects start to appear. As it was observed within the results from the calibrated Framingham formula, it seems that the impact of HDL-C levels on coronary risk was higher in women than in men, observations that need further evaluation in our locality due to lower HDL-C overall concentrations (**Table 3**).

In regards to the pathogenic importance of mixed dyslipidemia, where the common denominator is enhanced metabolism of lipids in the liver, associated with increased catabolism of Apo B-100 classes and subsequent enhancement of triglycerides with a concomitant decrease in HDL-C [43]. This scenario is of importance when preparing for appropriate treatment which has to treat two targets, being fibric acid derivatives the drugs of choice [43]. In a previous publication, we dealt with the pharmacological management of isolated low HDL-C, suggesting that physiologically niacin, fibrates and statins are all good choices to treat these cases, yet the hope is in the future for other drug-targeted medication to try and normalize this lipoprotein without the burden of serious side effects [44].

Lastly, the role of HDL-C in cardiovascular risk has been analyzed, proven and put into work in several risk score systems, including the Framingham-Wilson 10yr-coronary risk score [45,46]. Our study shoes that the difference between coronary risks in women with and without Low HDL-C levels was more pronounced in women than in men, results similar to those discussed by Mosca et al. [47] during the Guidelines for Prevention of CVD in women. The importance of this epidemiological finding in our population, which is obesity-burdened (48) with high prevalence of low grade inflammation [49,50], is that increasing HDL-C levels by 10 mg/dL reduces CVD risk by 2-3% [51]; therefore proper detection strategies need to be implemented to accurately analyze HDL-C and related classic and novel cardiometabolic risk factors and their impact on CVD risk projection.

Our findings also demonstrate that there are certain groups with clinical interest due to highest risk for dyslipidemia such as the case of unemployed Amerindian women, as well as subjects from both genders who have abdominal obesity and hypertriacylglyceridemia. These variables showed close relationship with the presence of Low HDL-C in the univariant and multivariant analysis. Early diagnosis of such states would allow the implementation of proper pharmacological therapy and necessary life style changes.

Among the limitations of this study, it´s the cross sectional nature and applications of it, which restrain us from procuring proper causality. First of all, it is necessary to confront these results with proper nutritional assessment. Nutrition quality is considered one of the many facets to evaluate when describing HDL-C tendencies within a population. The city of Maracaibo is well-known for its high-calories diets [52] and obesity problem [48] which would influence HDL-C in our city, and such avenue will be evaluated within the following branch of our MMSPS (currently being undertaken). Secondly, there´s the issue of ethnicity which would also influence the different prevalences observed, which will be further evaluated in this

population, especially after confirmation that carotid intima media-thickness is associated with HDL-C in Hispanics [53]. Finally, a third branch of the MMSPS regarding lipidomics and lipid profiling is currently undergoing, describing local SNPs and their impact in metabolic phenotypes [54].

Considering the rising prevalence of Low HDL-C Syndrome in our population, the influence that several factors cast on it and their relation to CVD and metabolic diseases, a profound analysis of these aspects is mandatory, especially in a country and state where CVD is the leading cause of death. The high prevalence of Low HDL-C levels and the resulting overall diminished percentiles of HDL-C (**Table 3**) suggest that current worldwide proposed HDL-C cutpoints [21,25] might not appropriate to our population, which is a highly admixtured [55,56] and subject to strong genetic influence [15]. For this reason population-specific HDL-C cut-off values should be of great priority because these ethnic differences render current criteria for classification and diagnosis for Low HDL-C unfit. The information gathered from these endeavors will provide the tools to develop appropriate primary and secondary preventive strategies to minimize risk, long-term disability and death.

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Conflict of Interests

There are no financial or other contractual agreements that might cause conflict of interests.

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