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Reference values for the triglyceride to high-density lipoprotein ratio and its association with cardiometabolic diseases in a mixed adult population: The ELSA-Brasil study

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KEYWORDS
Triglycerides;
High-density lipoprotein cholesterol;
TG/HDL-C ratio;
Reference values;
Cardiometabolic diseases

BACKGROUND: Among several lipid ratios available, the triglyceride/HDL-cholesterol (TG/HDL-C) may detect individuals at risk of cardiometabolic diseases. However, its reference values for different ethnicities are not well established.

OBJECTIVE: To define sex- and ethnicity-specific reference values for TG/HDL-C ratio in a large sample of healthy multiethnic adults and test its association with cardiometabolic conditions.

METHODS: An apparently healthy sample ($n = 2,472$), aged 35–74, free of major cardiovascular risk factors, was used to generate the reference values for the TG/HDL-C. Exclusion criteria were diabetes, elevated blood pressure, obesity, hypercholesterolemia, severe hypertriglyceridemia, and smoking history. Cut-offs based on the reference values were tested in the whole ELSA Brasil study ($n = 13,245$), stratified by sex and ethnicity, to identify cardiometabolic conditions.

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RESULTS: TG/HDL-C ratio was higher in men than women, and did not change significantly with age, regardless of sex and ethnicity. Also, black individuals showed lower levels of TG/HDL-C as compared to other ethnic groups. ROC curve showed that the cut-off based on the 75th percentile displayed better sensitivities and specificities for men and women, regardless of ethnicity. Also, the sex- and ethnicity-specific cut-offs based on the 75th percentile were significantly associated with all tested cardiometabolic conditions (hypertension, diabetes, obesity, metabolic syndrome, and insulin resistance). Also, we observed that the use of a single sex-specific cut-off (men: 2.6; women: 1.7) could be used for the different ethnicities with good reliability.

CONCLUSION: The defined TG/HDL-C cut-offs (men: 2.6; women: 1.7) are reliable and showed good clinical applicability to detect cardiometabolic conditions in a multiethnic population.
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Introduction

Elevated plasma triglycerides (TG) and decreased high-density lipoprotein cholesterol (HDL-C), along with the presence of abdominal obesity, elevated blood pressure, and increased plasma glucose levels are the most frequently recommended diagnostic criteria for Metabolic Syndrome (MetS).[1] MetS prevalence is increasing worldwide, and one of its most important clinical outcomes are cardiovascular diseases (CVD),[1] accounting for about 30% of all global deaths.[2]

Atherogenic dyslipidemia is usually associated with ectopic fat accumulation (increased intracellular lipid concentrations), which can alter the insulin signaling pathways, leading to an insulin-resistance scenario and a consequent increased risk of diabetes and other cardiometabolic disturbances.[3] Additionally, plasma lipoproteins interact with the artery wall cells contributing to atheroma plaque formation, which is the main cause of myocardial infarction and other important vascular events.[4,5]

Clinicians and the scientific community have been searching for biomarkers for the detection and/or prevention of cardiometabolic diseases.[6] Among the main risk biomarkers, lipid parameters (including TG, HDL-C, and low-density lipoprotein-cholesterol (LDL-C)) have been used for individual risk stratification for CVDs.[6] However, studies have evidenced that the use of plasma lipids ratios could be more accurate for risk detection of several conditions as compared to their isolated components.[7,8] Among the parameters evaluated to screen the cardiometabolic risk, the TG/HDL-C ratio is a valuable option due to its low cost, easy access, and moderate association with more specific markers of insulin resistance such as the hyperinsulinemic-euglycemic clamp.[4,9]

Gerald Reaven and colleagues introduced in 2003 the TG/HDL-C ratio, also known as Reaven's ratio, as a predictor of insulin resistance.[10] Since then, Reaven and colleagues made several other important contributions, proposing that races/ethnicities and sex must be taken into consideration to define the TG/HDL-C ratio cutoff values.[11,12] Comparisons between the TG/HDL-C ratio and MetS criteria to detect individuals at cardiometabolic risk,[13,14] and its combination with other parameters, such as waist circumference and body mass index (visceral adiposity index), evidenced that an altered TG/HDL-C ratio is an independent and very efficient risk predictor.[15] Later, Wakabayashi and Daimon evaluated the cardiometabolic risk by different TG/HDL-C cut-off values. In their study, a summary of the TG/HDL-C cut-offs used in more than 20 studies is given, highlighting the huge discrepancy among studies' stratification values. For instance, cut-offs varied from 1.4 to 4.7 in men and 1.4 to 3.76 in women from different populations.[16] Also, the studies used different methodological approaches to determine those values, hindering the results standardization, avoiding comparison, and difficulting their use in the clinical practice.

In this perspective, the establishment of reliable reference values for the TG/HDL-C ratio could help clinicians in the prevention, diagnosis, and management of cardiometabolic disorders. Therefore, we aimed in defining the sex- and ethnicity-specific reference values for TG/HDL-C based on a large sample of healthy mixed adults extracted from the ELSA-Brasil study. Giving a large number of participants in this cohort, we were able to use rigorous criteria to define a healthy subsample to obtain the reference values and to test the performance of these cut-offs to screening subjects at risk of cardiometabolic diseases in the whole cohort.

Methods

Study population and the establishment of a healthy sample

Data were obtained from baseline exams of the ELSA-Brasil cohort which is a multicenter study in adult public servants from six different Brazilian university institutions from three Brazilian regions. The data were collected from 2008 to 2010 and detailed information on the protocols from sampling and exams were previously published.[17,18] All participants gave written informed consent, and the ELSA-Brasil study was approved by the ethical committees of the six institutions where participants were recruited.

The cohort included 15,105 volunteers aged 35–74 years old. To select an apparently healthy sample from the entire cohort, we applied the all following exclusion criteria: the presence of diabetes (fasting glucose levels $\geq$126 mg/dL, or Hb1Ac $\geq$6.5%, or 2 h post-load plasma glu-

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cose ≥200 mg/dL, or in use of any glucose-lowering drug); the presence of elevated blood pressure (systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or in use of any blood pressure-lowering drug); the presence of overweight or obesity (body mass index ≥25 kg/m^2); the presence of central obesity (waist circumference ≥ 88 cm for women and 102 cm for men); total cholesterol levels ≥ 240 mg/dL; severe hypertriglyceridemia (triglycerides >400 mg/dL), and individuals with smoking history. We also excluded those participants with self-reported previous cardiovascular disease ($n = 1,186$).

The ethnicity of each participant was self-declared, and they were asked the following question: "The Brazilian census (IBGE) describes people's skin color or race as "Black", "Brown", "White", "Asian descendant" or "native Brazilian". If you were to answer the IBGE census today, how would you describe your skin color or race?" Thus, they were stratified as white, black, brown, indigenous (native Brazilian), or Asiatic. The category Brown (sometimes called "Pardos") is used to refer to Brazilians of varied ethnic ancestry. For this study, we also excluded subjects without an ethnic classification ($n = 184$) and those with a small frequency in the study (indigenous [$n = 157$] and Asiatic [$n = 374$]).

Measurements

For the data collection, participants were asked to fast for a period from 10 – 14 hours, and do not consume alcohol neither perform physical exercises in the 24 hours before the exams. Anthropometric data, including body weight (Kg), height (cm), and waist circumference (cm) were collected while the participants were fasting.

Smoking status was defined based on two categories: those who never smoke, or those who are former and current smokers. Physical activity was classified as insufficient, or moderate/vigorous based on the long version of the International Physical Activity (IPAC) Questionnaire.

Blood samples were drawn for the assessment of biochemistry and lipid profiles. Standard protocols were used to assess the blood levels of total cholesterol, TG, and HDL-C. TG (mg/dL) to HDL-C (mg/dL) ratio was obtained by the formula (TG/HDL-C).[19,20] The Friedwald formula was used to assess LDL-C levels, if TG < 400 mg/dL. The Homeostasis Model Assessment for Insulin Resistance (HOMA-IR) was calculated according to the following formula: (fasting glucose levels x fasting insulin levels)/405. The CDK-EPI formula was applied to estimate the glomerular filtration rate (eGFR).

Systolic and diastolic blood pressure (SBP, DBP) and heart rate (HR) were measured using an oscillometric device (Omron HEM 705 CPINT, Japan). Three readings were obtained at 1–2 min intervals, and the clinic blood pressure was set as the average of the last two measurements. Hypertension was defined as SBP ≥140 mmHg or DBP ≥90 mmHg or the use of any blood pressure-lowering drug.

MetS was defined following the modified ATP III criteria[21,22] when any three of the five factors were present: WC ≥ 102 cm in men and ≥ 88 cm in women; fasting glucose >100 mg/dL or drug treatment for elevated glucose; HDL-C <40 mg/dL in men and 50 mg/dL in women; TG ≥150 mg/dL; SBP ≥130 mmHg or DBP ≥85 mm Hg, or the use of blood pressure-lowering drugs.

Statistical analysis

The data are described as mean ± standard deviation or the absolute frequency and percentage for categorical variables. The goodness-of-fit to a Gaussian distribution was verified using the Kolmogorov-Smirnov test. To verify the differences between clinical and anthropometric parameters among different ethnicities, a one-way analysis of variance (ANOVA) was used. In the case of a significant F test, Bonferroni's post hoc was applied to find specific intergroup differences. To compare the frequency of categorical variables among ethnicities, we used the Chi-squared test.

The sex- and ethnicity-specific TG/HDL-C percentiles (5th, 10th, 25th, 50th, 75th, 90th, and 95th) were obtained, and we build percentiles curves based on the quantile regression model. To verify the association between TG/HDL-C percentiles and diabetes, HOMA-IR, hypertension, obesity, increased WC, and MetS in the total ELSA-Brasil sample (13,245 individuals), we performed a multiple logistic regression to obtain the adjusted odds ratio and the respective 95% confidence interval (CI). Finally, the Receiver Operating Characteristic Curves (ROC) were obtained to assess the specificity and sensitivity of the percentiles generated with the healthy sample to predict cardiometabolic conditions.

All statistical analyses were performed using SPSS 22.0 statistical package (SPSS, Chicago, IL). Statistical significance was set at $P < 0.05$.

Results

From the whole ELSA-Brasil cohort (15,105 individuals, 35–74 years) we excluded 1,186 participants with self-reported CVD at baseline (myocardial infarction, stroke, coronary artery bypass grafting or coronary stents, cardiac valvular diseases). Other 10,856 were excluded because the presence of at least one of the following factors: diabetes ($n = 2,973$), elevated blood pressure ($n = 5,416$), overweight/obesity ($n = 9,675$), increased WC ($n = 5,431$), increased total cholesterol levels ($n = 3,779$), TG > 400 mg/dL ($n = 259$), and smoking history ($n = 591$). The final healthy sample comprised 2,472 participants (968 men and 1,504 women) which the clinical and anthropometric characteristics are shown in Table 1 stratified by sex and ethnicity. The mean age was 48.2 ± 8.7 in men, and 47.7 ± 8.1 in women. It is noteworthy that some differences were observed among ethnic groups (Table 1). High HDL-C and low TG levels (although not statistically significant) were found in black men. Also, black women showed lower TG levels compared to the other ethnic groups. Those results explain the lower TG/HDL-C ratio in both black men and women (Table 1).

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Table 1 Clinical and anthropometric characteristics of healthy men and women stratified by ethnicity.

	MEN					WOMEN				
	White(n = 576)	Brown(n=295)	Black(n=97)	p-value	All(n=968)	White(n=974)	Brown(n=360)	Black(n=170)	p-value	All(n=1504)
Age (years)	49.31 ± 9.00	46.63 ± 8.14*	46.81 ± 8.16*	<0.001	48.25 ± 8.75	48.31 ± 8.28	46.15 ± 7.30*	47.32 ± 7.92	<0.001	47.68 ± 8.06
Height (cm)	173.95 ± 7.07	172.12 ± 7.10*	172.75 ± 6.45	0.001	173.27 ± 7.07	160.68 ± 6.21	159.93 ± 6.13	160.26 ± 6.05	0.134	160.45 ± 6.18
Weight (Kg)	68.83 ± 7.60	67.16 ± 7.75*	66.84 ± 7.60	0.002	68.12 ± 7.68	57.40 ± 5.95	57.28 ± 6.32	58.10 ± 6.20	0.313	57.45 ± 6.07
BMI (Kg/m^2)	22.71 ± 1.78	22.62 ± 1.75	22.37 ± 2.01	0.215	22.65 ± 1.80	22.21 ± 1.77	22.36 ± 1.77	22.59 ± 1.65*	0.028	22.29 ± 1.76
WC (cm)	84.06 ± 6.45	82.79 ± 6.16*	81.08 ± 7.11*	<0.001	83.37 ± 6.49	75.78 ± 5.72	76.46 ± 5.94	76.31 ± 5.44	0.120	76.00 ± 5.75
Glucose (mg/dL)	102.80 ± 7.01	102.69 ± 7.91	101.06 ± 9.20	0.105	102.59 ± 7.54	98.39 ± 7.41	98.33 ± 7.38	98.65 ± 7.97	0.892	98.40 ± 7.46
Insulin (UI)	7.89 ± 3.65	7.91 ± 3.59	7.27 ± 3.85	0.285	7.83 ± 3.65	7.76 ± 3.93	7.64 ± 3.18	7.84 ± 3.35	0.820	7.74 ± 3.71
HOMA-IR	1.92 ± 0.91	1.92 ± 0.92	1.75 ± 0.99	0.243	1.90 ± 0.92	1.81 ± 0.95	1.78 ± 0.79	1.83 ± 0.84	0.790	1.80 ± 0.90
TC (mg/dL)	195.10 ± 26.68	194.65 ± 27.03	191.32 ± 29.63	0.445	194.58 ± 27.09	197.22 ± 25.30	195.59 ± 27.44	194.42 ± 28.10	0.326	196.51 ± 26.15
LDL-C (mg/dL)	121.25 ± 24.05	119.05 ± 24.27	114.47 ± 24.73*	0.023	120.16 ± 24.13	114.52 ± 22.24	115.49 ± 23.14	113.92 ± 26.45	0.710	114.68 ± 22.96
HDL-C (mg/dL)	52.55 ± 10.93	52.92 ± 12.10	58.06 ± 14.65*#	<0.001	53.21 ± 11.81	64.98 ± 13.78	62.44 ± 13.57*	64.16 ± 13.20	0.011	64.95 ± 13.73
TG (mg/dL)	106.34 ± 50.53	108.26 ± 56.55	96.26 ± 51.75	0.143	105.92 ± 52.60	85.69 ± 38.83	86.51 ± 35.42	77.50 ± 34.65*#	0.022	84.96 ± 37.65
TG/HDL-C ratio	2.19 ± 1.33	2.22 ± 1.44	1.85 ± 1.34	0.059	2.16 ± 1.37	1.38 ± 0.78	1.46 ± 0.81	1.28 ± 0.86#	0.047	1.39 ± 0.80
Uric acid (mg/dL)	5.74 ± 1.03	5.63 ± 1.09	5.68 ± 1.03	0.345	5.70 ± 1.05	4.17 ± 0.85	4.07 ± 0.82	4.05 ± 0.89	0.062	4.13 ± 0.85
GFR (mL/min per 1.73 m^2)	85.73 ± 13.82	86.95 ± 13.48	85.77 ± 13.38	0.447	86.10 ± 13.67	105.46 ± 11.19	107.52 ± 10.40*	104.66 ± 11.38#	0.003	105.86 ± 11.06
SBP (mmHg)	114.96 ± 10.22	116.35 ± 10.42	118.41 ± 9.52*	0.004	115.73 ± 10.26	107.23 ± 10.64	108.09 ± 11.35	110.16 ± 10.76*	0.004	107.77 ± 10.86
DBP (mmHg)	72.10 ± 7.58	72.93 ± 7.50	73.66 ± 7.16	0.085	72.51 ± 7.53	67.59 ± 7.72	69.20 ± 7.70*	70.38 ± 8.38*	<0.001	68.29 ± 7.85
HR (bpm)	67.56 ± 9.60	67.42 ± 9.85	66.51 ± 10.35*#	0.017	67.21 ± 9.78	71.68 ± 9.44	71.41 ± 9.43	70.59 ± 9.08	0.384	71.49 ± 9.40
Physical Activity	-	-	-	0.052	-	-	-	-	<0.001	-
Insufficient	362 (64.0)	204 (70.1)	72 (66.9)		638 (66.9)	663 (69.4)	283 (79.9)	134 (79.8)		1080 (73.1)
Moderate/ Vigorous	204 (36.0)	87 (29.9)	316 (33.1)		316 (33.1)	292 (30.6)	71 (20.1)	34 (20.2)		397 (26.9)

BMI: Body Mass Index; WC: Waist Circumference; HOMA-IR: Homeostasis Model Assessment for Insulin Resistance; TC: Total Cholesterol; LDL: Low-density Lipoprotein; HDL: High-density Lipoprotein; TG: Triglycerides; GRF: Glomerular Filtration Rate; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HR: Heart Rate. * $P < 0.05$ vs. white; # $P < 0.05$ vs. brown.

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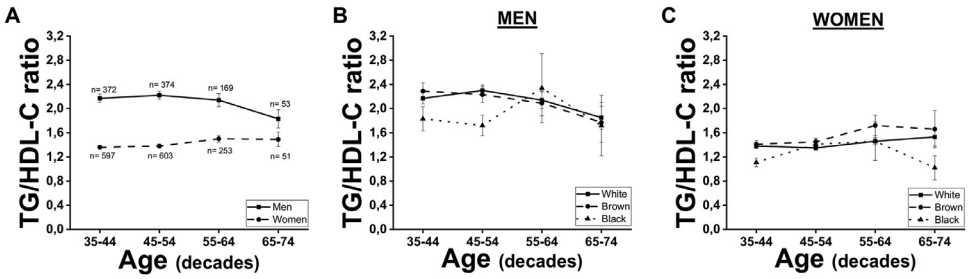

Figure 1 Panel A shows TG/HDL-C ratio by age categories stratified by sex. The changes in the TG/HDL-C ratio with age were also stratified by ethnicity in men (panel B) and women (panel C).

Table 2 Sex- and ethnicity-specific percentiles for the TG/HDL-C ratio in a healthy adult sample.

TG/HDL-C ratio	MEN				TG/HDL-C ratio	WOMEN			
	Ethnicity					Ethnicity			
	White (n = 576)	Brown (n=295)	Black (n=97)	ALL (n=968)		White (n=974)	Brown (n=360)	Black (n=170)	ALL (n=1504)
5th	0.81	0.85	0.61	0.79	**5th**	0.58	0.61	0.59	0.59
10th	0.95	0.95	0.74	0.92	**10th**	0.67	0.72	0.67	0.68
25th	1.25	1.24	0.98	1.22	**25th**	0.87	0.95	0.79	0.88
50th	1.82	1.87	1.38	1.79	**50th**	1.20	1.27	1.05	1.21
75th	2.65	2.72	2.19	2.63	**75th**	1.67	1.72	1.45	1.67
90th	3.84	4.10	3.94	3.93	**90th**	2.27	2.39	2.05	2.29
95th	5.17	5.20	4.75	5.14	**95th**	2.98	3.14	2.67	2.97

TG: triglycerides; HDL-C: High-density Lipoprotein.

We also evaluated whether the TG/HDL-C ratio varies with age in healthy subjects stratified by sex and ethnicity. Despite the higher TG/HDL-C values in men for all age categories, it did not change significantly with age, regardless of sex or ethnicity (Fig. 1A-C). Thus, we established the sex- and ethnicity-specific percentiles for the TG/HDL-C ratio in the healthy sample (Table 2 and Fig. 2).

To test if any of the sex- and ethnicity-specific TG/HDL-C percentiles would be suitable to identify cardiometabolic conditions, we applied those cut-offs for the entire ELSA-Brasil population (n = 13,245), without individuals with self-reported cardiovascular disease, severe hypertriglyceridemia, and classified as indigenous or Asiatics, to define participants below and above those specific limits and their association to cardiometabolic conditions. The clinical and anthropometric characteristics of the large cohort sample are shown in Supplementary Table S1. The ROC analysis provided the sensitivities and specificities of some TG/HDL-C percentiles in identifying diabetes, HOMA-IR, hypertension, obesity, increased WC, and MetS for men and women, as well as for all tested ethnicities (Supplementary Table S2). As observed in Supplementary Table S2, the sex-specific value based on the 75th percentile (overall men: 2.6; overall women: 1.7) showed better sensitivities and specificities over the different cardiometabolic conditions when compared to other percentiles, even when stratified by ethnicity. Thus, based on their stable sensitivities and specificities (Table 3) we used the sex- and ethnicity-specific 75th percentile as the TG/HDL-C ratio cut-off to test its association with the cardiometabolic conditions.

Table 4 shows that the sex- and ethnicity-specific cut-offs based on the 75th percentile for the TG/HDL-C ratio were significantly associated with all tested cardiometabolic conditions, except for hypertension in black men. Indeed, although significant, the association between TG/HDL-C and hypertension and diabetes was lower in blacks than in whites and browns. We also tested the association between TG/HDL-C and WC based on different available cut-offs (102 and 88, or 90 and 80, for men and women, respectively), and the odds ratio remained significant for both WC cut-offs.

As expected, the highest odds ratio was found for the association between TG/HDL-C ratio and MetS. To avoid the effect of high TG and low HDL-C levels in the definition of MetS, we excluded individuals with altered TG and HDL-C, and classified MetS based only on the other remaining parameters (elevated blood pressure, increased WC, and increased fasting glucose). We observed that the sex- and ethnicity-specific values based on the 75th percentile can predict MetS even when the TG and the HDL-C are not present in the diagnosis criteria (data not shown).

Finally, when we applied the unique sex-specific cut-off (generated without stratification for ethnicity; overall men: 2.6; overall women: 1.7) for white, brown, and black participants, the results were pretty much the same(Table 5), sug-

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Table 3 Sensitivities and specificities for different TG/HDL-C ratio cutoffs in identifying cardiometabolic conditions

	MEN			WOMEN		
	Cutoff	Sensitivity (%)	Specificity (%)	Cutoff	Sensitivity (%)	Specificity (%)
Diabetes						
White	**2.65**	67.73	51.95	**1.67**	76.42	52.92
Brown	**2.72**	(63.9–71.4)	(50.0–53.9)	**1.72**	(72.4–80.1)	(51.2–54.6)
Black	**2.19**	64.23	55.12	**1.45**	72.24	51.38
All	**2.63**	(59.3–69.0)	(52.5–57.7)	**1.67**	(67.0–77.1)	(49.0–53.8)
HOMA-IR		64.23	47.63		74.47	51.52
White	**2.65**	(57.9–70.2)	(43.6–51.7)	**1.67**	(69.4–79.1)	(48.4–54.6)
Brown	**2.72**	65.09	65.09	**1.72**	73.02	53.43
Black	**2.19**	(62.4–67.7)	(62.4–67.7)	**1.45**	(70.3–75.6)	(52.2–54.7)
All	**2.63**			**1.67**		
Hypertension		75.30	55.81		78.97	56.99
White	**2.65**	(72.1–78.3)	(53.8–57.8)	**1.67**	(76.0–81.7)	(55.2–58.8)
Brown	**2.72**	72.91	58.35	**1.72**	80.65	57.80
Black	**2.19**	(68.2–77.2)	(55.7–60.9)	**1.45**	(76.9–84.1)	(55.2–60.3)
All	**2.63**	75.85	50.93	**1.67**	80.61	55.05
Obesity		(69.4–81.5)	(47.0–54.8)		(76.1–84.6)	(51.9–58.2)
White	**2.65**	73.87	56.43	**1.67**	78.20	58.01
Brown	**2.72**	(71.4–76.2)	(55.0–57.9)	**1.72**	(76.1–80.2)	(56.7–59.3)
Black	**2.19**			**1.45**		
All	**2.63**	60.92	52.86	**1.67**	70.15	55.70
Waist		(58.0–63.8)	(50.7–55.0)		(67.2–73.0)	(53.9–57.5)
Circumference	**2.65**	56.82	55.75	**1.67**	65.21	53.72
White	**2.72**	(53.1–60.5)	(52.8–58.7)	**1.72**	(61.4–68.9)	(51.0–56.4)
Brown	**2.19**	60.76	49.08	**1.45**	64.07	52.93
Black	**2.63**	(55.9–65.4)	(44.3–53.9)	**1.67**	(60.1–67.9)	(49.2–56.6)
All		58.71	53.71		65.22	55.75
MetS ATP III	**2.65**	(56.6–60.8)	(52.1–55.3)	**1.67**	(63.2–67.2)	(54.4–57.1)
White	**2.72**			**1.72**		
Brown	**2.19**	70.77	52.74	**1.45**	77.25	56.41
Black	**2.63**	(67.1–74.3)	(50.8–54.7)	**1.67**	(74.2–80.0)	(54.6–58.2)
All		64.33	54.61		70.53	53.52
		(59.1–69.3)	(52.0–57.2)		(66.3–74.5)	(51.0–56.0)
		70.77	48.72		68.66	52.50
		(63.8–77.01)	(44.9–52.6)		(64.2–72.8)	(49.1–55.8)
		67.91	53.27		70.60	55.80
		(65.2–70.6)	(51.8-54.7)		(68.4–72.7)	(54.5–57.1)
		71.00	55.18		72.01	63.09
		(67.7–74.1)	(53.1-57.2)		(69.6–74.3)	(61.1–65.0)
		66.12	55.58		68.49	61.08
		(61.0–71.0)	(53.0–58.2)		(65.3–71.6)	(58.1–64.0)
		73.89	49.47		69.71	62.14
		(66.8–80.1)	(45.6–53.4)		(66.2–73.1)	(58.2–66.0)
		69.47	55.04		68.58	63.21
		(66.9–71.9)	(53.6–56.5)		(66.9–70.2)	(61.7–64.7)
		85.15	66.92		86.22	64.82
		(82.9–87.2)	(64.8–69.0)		(84.0–88.2)	(63.0–66.6)
		83.06	69.77		83.51	65.08
		(79.8–86.0)	(67.0–72.4)		(80.5–86.2)	(62.3–67.7)
		85.81	63.78		81.25	63.08
		(81.4–89.5)	(59.4–68.0)		(77.5–84.6)	(59.6–66.5)
		84.41	68.33		83.31	65.97
		(82.7–86.0)	(66.8–69.9)		(81.7–84.8)	(64.6–67.3)

TG: triglycerides; HDL–C: High-density Lipoprotein; MetS: Metabolic Syndrome; ATP III: National Cholesterol Education Program's Adult Treatment Panel III; HOMA-IR: Homeostasis Model Assessment – Insulin Resistance.

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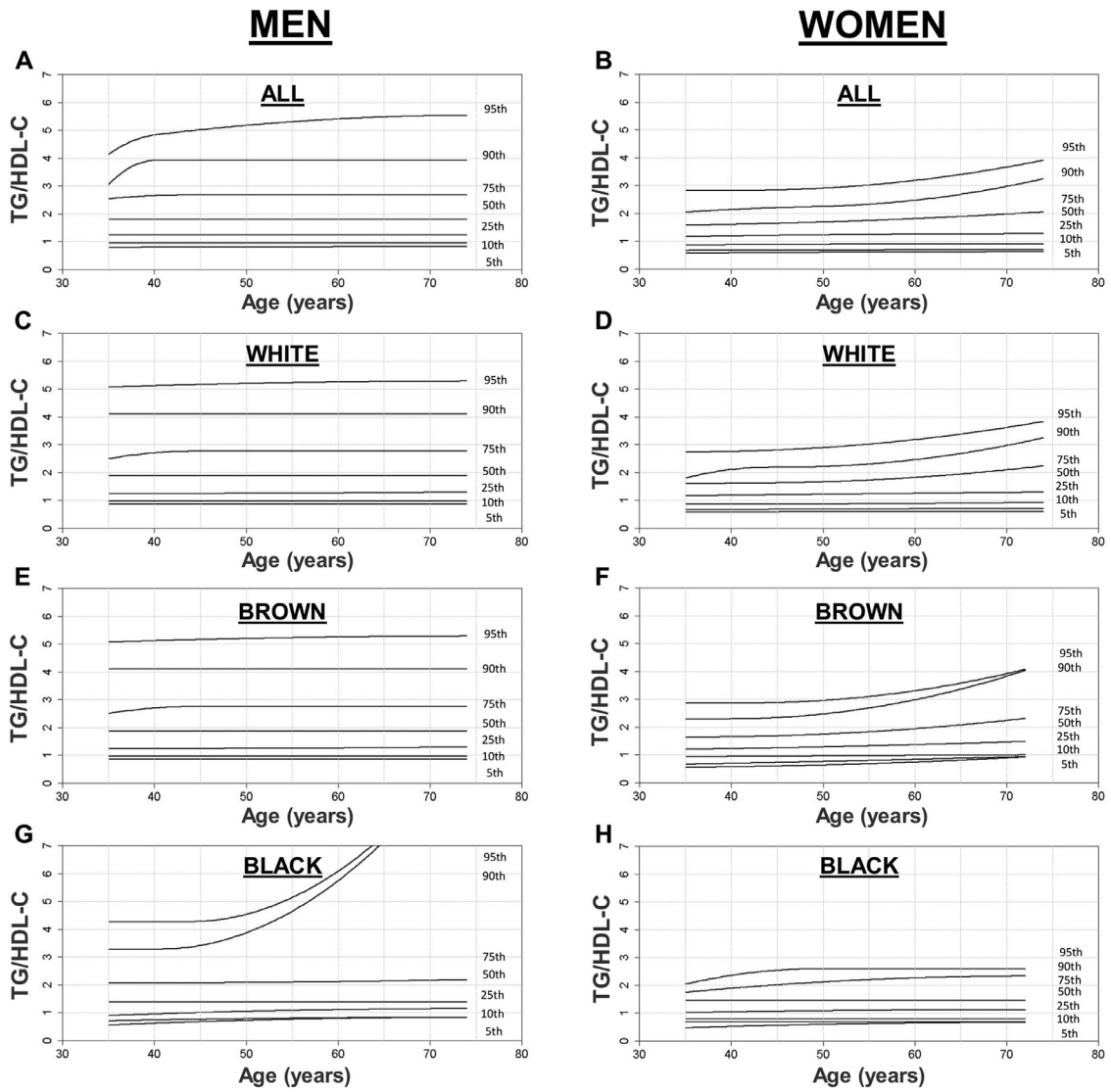

Figure 2 Percentile curves for the TG/HDL-C in healthy men (A) and women (B). Also, percentile curves were defined for different ethnicities (C – H).

gesting that the sex-specific cut-off based on the 75th percentile (men: 2.6; women: 1.7) may be an interesting single screening value for the aforementioned conditions even when ethnicity is considered.

Discussion

The present study aimed to define a TG/HDL-C ratio reference value for predicting cardiometabolic conditions for men and women of different ethnicities. We showed that the cut-offs extracted from the sex- and ethnicity-specific reference values for TG/HDL-C defined in our study showed good sensitivities and specificities, and were significantly associated with some cardiometabolic conditions (hypertension, diabetes, obesity, MetS, and insulin resistance). Also, we observed that the use of a single sex-specific cut-off (men: 2.6; women: 1.7) could be used for the different ethnicities with good reliability.

Since their first descriptions, Reaven and colleagues also published studies showing the ability of TG/HDL-C ratio to detect other conditions, such as increased blood pressure and its ability to detect a group of hypertensive and normotensive individuals with greater cardiovascular risk,[23] adverse lipid profile, impaired insulin sensitivity, increased C-reactive protein levels,[24] and also to better identify prediabetic individuals with normal glucose levels who need more intense therapeutic intervention regarding cardiovascular risk assessment.[25] Indeed, efforts have been done by several authors to understand the ability of the TG/HDL-C ratio to help clinicians in implementing more intense therapeutic care to individuals at risk but commonly underdiagnosed.

It was already shown in other studies that lipid ratios seem better markers for risk prediction than their isolated components.[26,27] The TG/HDL-C ratio, in particular, displays some interesting characteristics. First, TG and HDL-C measurements are already standardized and routinely measured in the clinical practice,[11,28] as compared with other parame-

Table 4 Multiple logistic regression for the association of TG/HDL-C and some cardiometabolic conditions using sex- and ethnicity-specific cutoffs.

	MEN			WOMEN		
	Adjusted OR (95%CI)			Adjusted OR (95%CI)		
	White(cutoff 2.65)	Brown(cutoff 2.72)	Black(cutoff 2.19)	White(cutoff 1.67)	Brown(cutoff 1.72)	Black(cutoff 1.45)
Diabetes	1.99	1.93	1.44	2.26	1.93	2.42
HOMA-IR	(1.63–2.43)	(1.51–2.48)	(1.04–2.01)	(1.79–2.87)	(1.45–2.57)	(1.79–3.27)
Hypertension	3.09	3.35	2.71	3.00	4.48	4.03
Obesity	(2.51–3.80)	(2.54–4.42)	(1.86–3.96)	(2.45–3.67)	(3.44–5.81)	(2.95–5.49)
WC	1.51	1.44	1.31	2.07	1.56	1.44
MetS ATP III	(1.28–1.79)	(1.16–1.77)	(0.97–1.76)	(1.74–2.45)	(1.25–1.94)	(1.12–1.85)
	2.19	1.72	2.06	3.43	2.29	2.00
	(1.79–2.66)	(1.34–2.22)	(1.44–2.94)	(2.85–4.13)	(1.82–2.88)	(1.56–2.57)
	2.51	1.95	2.48	3.36	2.80	3.13
	(2.09–3.03)	(1.51–2.51)	(1.69–3.63)	(2.89–3.90)	(2.29–3.42)	(2.46–3.98)
	12.98	12.34	10.98	10.86	9.18	7.58
	(10.63–16.12)	(9.52–16.12)	(7.51–15.87)	(8.92–13.15)	(7.19–11.71)	(5.71–10.06)

Diabetes was adjusted by age, hypertension, overweight/obesity, and physical activity. Hypertension was adjusted by age, diabetes, overweight/obesity, and physical activity. Obesity was adjusted by age, diabetes, hypertension, and physical activity. Waist circumference was adjusted by age, diabetes, hypertension, and physical activity. MetS was adjusted by age and physical activity. HOMA-IR was adjusted by age, hypertension, overweight/obesity, and physical activity. WC: Waist Circumference; MetS: Metabolic Syndrome; ATP III: National Cholesterol Education Program's Adult Treatment Panel III; HOMA-IR: Homeostasis Model Assessment – Insulin Resistance.

ters used, such as fasting insulin, and HOMA-IR. Also, their measurements are not examiner-dependent, as observed with other variables (e.g. WC). Lastly, elevated TG and decreased HDL-C rarely occur as isolated disorders, thus consistently pointing towards metabolic alterations.[29]

The TG/HDL-C ratio was already reported to be positively associated with several cardiometabolic disorders, including type 2 diabetes mellitus, coronary heart disease, myocardial infarction, unstable angina, and others.[28,30–32] Moreover, the definition of a TG/HDL-C reference value goes beyond its ability to detect individuals with cardiometabolic conditions. The so-called atherogenic dyslipidemia is highly frequent due to the obesity epidemics and favors the development of atherosclerosis.[33] Also, the TG/HDL-C ability to predict insulin resistance, which is not easily diagnosed by the currently used methods (mainly based on insulin levels detection), supports this ratio as an important cardiometabolic risk predictive marker.[34]

The literature lacks a consensus on optimal TG/HDL-C cut-off values to be used in clinical practice for predicting the risk of cardiometabolic conditions. Several studies attempted to define this normal range, however, the values provided vary significantly.[10,35–40] Some authors use the 3.0 cut-off, which is mainly the average upper limit reference value of TG (150 mg/dL) divided by the average lower limit reference for the HDL-C (50 mg/dL), displaying positive associations with cardiovascular risk, and MetS.[10,3941] However, as the majority of studies define the TG/HDL-C ratio cut-off values based on ROC analyses, several different cut-off values are described in the literature. Values such as 4.04 for men and 2.86 for women, on an Iranian adult population;[36] 2.75 for men and 1.65 for women, on a Spanish adult population;[37] 2.8 for men and 1.9 for women; 3.52 for both, on a Korean apparently healthy adult population;[42] and others, were described as cut-off values for predicting MetS. Additional values are also described for the prediction of other disorders such as insulin resistance,[12] and cardiovascular diseases.[39,43] These differences in the TG/HDL-C cut-offs are attributed to several important factors. First, the influence of ethnicity,[44,45] which is known to have a direct effect on the TG, and HDL-C levels. Second, the sample size also varies considerably among studies, thus interfering with the statistical power of the cut-off value defined. Third, the criteria to define the outcome used in the cut-off generation, as exemplified by the several MetS criteria adopted worldwide.[46] Fourth, the baseline characteristics of the studied population included in these studies, and lastly, the methodology used on the TG/HDL-C cut-off definition, such as ROC, quartiles, tertiles, etc.

The literature is controversial regarding the definition of ethnicity-specific TG/HDL-C reference values. A few studies reported difficulties in generating specific TG/HDL-C reference values, especially for the black population (mainly African Americans).[47–49] Our study, on the other hand, based on a large mixed adult population was able to define ethnicity-specific (white, brown, and black) reference values and establish cut-offs that can be used to predict cardiometabolic conditions with good reliability for each ethnic group evaluated. However, an important achievement of our results was the proposition of a single sex-specific TG/HDL-C cut-off that can efficiently predict several cardiometabolic conditions across different ethnic groups. Similarly, Li et al.

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Table 5 Multiple logistic regression for the association of TG/HDL-C and some cardiometabolic conditions among different ethnicities using a single sex-specific cutoff (men: 2.6; women: 1.7).

	MEN				WOMEN			
	Odds ratio (95%CI)				Odds ratio (95%CI)			
	White	Brown	Black	All	White	Brown	Black	All
Diabetes	2.01	1.89	1.47	1.78	2.29	1.86	2.60	2.09
HOMA-IR	(1.64–2.46)	(1.47–2.43)	(1.06–2.02)	(1.55–2.05)	(1.81–2.89)	(1.40–2.48)	(1.96–3.46)	(1.80–2.43)
Hypertension	3.09	3.14	2.51	2.98	2.99	4.44	3.70	3.53
Obesity	(2.51–3.80)	(2.38–4.14)	(1.76–3.57)	(2.57–3.47)	(2.45–3.64)	(3.42–5.78)	(2.79–4.92)	(3.08–4.04)
WC	1.52	1.43	1.38	1.41	2.07	1.59	1.43	1.63
MetS ATP III	(1.28–1.80)	(1.16–1.77)	(1.02–1.87)	(1.25–1.58)	(1.74–2.45)	(1.28–1.98)	(1.12–1.84)	(1.46–1.83)
	2.30	1.68	1.96	2.04	3.35	2.26	1.69	2.42
	(1.89–2.81)	(1.30–2.17)	(1.40–2.74)	(1.77–2.35)	(2.79–4.01)	(1.80–2.84)	(1.32–2.15)	(2.14–2.72)
	2.59	1.96	2.20	2.39	3.31	2.84	2.76	2.95
	(2.15–3.13)	(1.51–2.53)	(1.54–4.68)	(2.08–2.74)	(2.85–3.84)	(2.33–3.48)	(2.16–3.52)	(2.66–3.28)
	13.37	12.87	12.26	12.65	11.18	9.24	8.85	9.43
	(10.86–16.46)	(9.81–16.89)	(8.63–17.41)	(10.91–14.67)	(9.23–13.54)	(7.23–11.83)	(6.73–11.62)	(8.30–10.73)

Diabetes was adjusted by age, hypertension, overweight/obesity, and physical activity. Hypertension was adjusted by age, diabetes, overweight/obesity, and physical activity. Obesity was adjusted by age, diabetes, hypertension, and physical activity. Waist circumference was adjusted by age, diabetes, hypertension, and physical activity. MetS was adjusted by age and physical activity. HOMA-IR was adjusted by age, hypertension, overweight/obesity, and physical activity. HOMA-IR: Homeostasis Model Assessment for Insulin Resistance; WC: Waist Circumference; MetS: Metabolic Syndrome; ATP III: National Cholesterol Education Program's Adult Treatment Panel III; HOMA-IR: Homeostasis Model Assessment – Insulin Resistance.

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using the NHANES data proposed the use of a single sex-specific TG/HDL-C cut-off value, with good reliability to predict hyperinsulinemia, regardless of ethnicity.[11]

An important controversial point is the influence of race/ethnicities on the ability of the TG/HDL-C ratio in predicting cardiometabolic risk, as conflicting data is found in the literature. The main difficulties rely especially on this ratio applicability in African Americans, which despite having higher cardiometabolic risk, present decreased TG levels, increased HDL-C, and acute insulin response.[11,50] This "healthier" lipid profile found in black individuals justifies the reluctance of establishing direct relationships between hypertriglyceridemia and insulin resistance and other cardiometabolic conditions. Sumner et al. were the first to investigate this influence, following Reaven's publication, on a more representative multiethnic population, and reported this ratio's inability to predict insulin resistance in African Americans.[47] Reaven and colleagues reported that this ratio can predict insulin resistance regardless of race/ethnicity, as long as different cutoffs are applied,[11] which was later partially corroborated by Sumner in other studies, where the TG/HDL-C ratio was able to identify insulin resistance in African men, but not in African women.[48] Later, other studies were published with conflicting results.[51–53] Most of the studies, however, tested the TG/HDL-C ratio in small samples, thus requiring more robust studies to eliminate other potential sources of bias.

In our study, we defined sex- and ethnicity-specific TG/HDL-C reference values, being those for black men and women smaller as compared to their white and brown counterparts. Also, the odds ratios for the association between TG/HDL-C and cardiometabolic conditions in blacks were lower than observed for other ethnicities. Indeed, the non-Hispanic black population has a lower prevalence of dyslipidemia as compared to other ethnic groups,[53] despite being more predisposed to develop hypertension, diabetes, and obesity as compared to white.[54] Also, black individuals usually present a lower prevalence of increased TG and decreased HDL-C,[55,56] as shown in our study. These differences might be based on a few aspects of the lipid metabolism: a differential expression of lipid-related enzymes, such as hepatic lipase (which is decreased in black individuals, and responsible for HDL-C clearance), and lipoprotein lipase (commonly increased in black individuals and responsible for TG clearance).[57] Additionally, individuals of African ancestry seem to have a greater acute insulin response, which stimulates lipoprotein lipase, and the clearance of free fatty acids,[58] and decreased levels of ApoCIII, an apolipoprotein attached to the surface of VLDL-C molecules that impairs TG clearance.[59]

An increased TG/HDL-C ratio can be the reflex or the cause of the metabolic consequences of insulin resistance. The resistance to the action of insulin has important effects on the adipose tissue, increasing lipolysis, and thus the free fatty acid efflux to the liver.[60] The increased amount of free fatty acids in the liver leads to hypertriglyceridemia, the TG assembly into VLDL-C, and transfer to HDL-C and LDL-C lipoproteins.[60] The HDL-C particles, however, are filled with more TG than usual, being more rapidly cleared from the circulation, and thus having their levels reduced, impairing the removal of cholesterol from the vasculature.[60] The opposite is also true, in which the ectopic lipid accumulation, which is commonly observed in certain conditions such as obesity, increases free fatty acids efflux to the liver, leading to aforementioned dyslipidemia, and thus insulin resistance.[3,61] Concomitantly, inflammatory pathways are usually overactivated in dyslipidemia/cardiometabolic conditions, impairing insulin signaling, and consequently leading to insulin resistance.[60,62] In fact, several studies already evidenced a clear association between the TG/HDL-C ratio and insulin resistance,[10,63] which is important, as insulin resistance is believed to be the underlying cause of several cardiometabolic alterations observed in individuals with diabetes, hypertension, dyslipidemia, and MetS.

Another important methodological point of our study was the use of the ROC curves to define the sensitivities and specificities for the sex- and ethnicity-specific cut-offs. In our study, the 75th percentile cut-off values (2.6 for men and 1.7 for women) were similar to the values described by Cordero et al. (2.75 for men, and 1.65 for women),[37] and Bibra et al. (2.8 for men, and 1.9 for women)[34] when the MetS was the outcome. The defined sex-specific cut-offs remained stable for all cardiometabolic conditions (not only MetS), regardless of the ethnic groups tested. The definition of sensitivities and specificities is important to express the test performance, which in our case, is the ability of the TG/HDL-C ratio to "rule out" and "rule in" negative and positive cases for all the cardiometabolic conditions evaluated.

Finally, the odds ratios obtained for the association between some cardiometabolic conditions and the sex- and ethnicity-specific cut-offs for the TG/HDL-C ratio were very satisfactory. Moreover, a unique sex-specific TG/HDL-C ratio value showed a similar association with all cardiometabolic conditions, regardless of ethnicity. Thus, these findings support the use of the 75th percentile-based reference value (2.6 for men and 1.7 for women) as a unique suitable sex-specific cut-off for a range of important cardiometabolic conditions with MetS included in a multiethnic population.

Several further limitations of the current analysis should be mentioned. Given the cross-sectional design of this analysis, reverse causation cannot be excluded. Also, due to a large number of stratification (sex and ethnicity) made on the healthy sample, the sample size was reduced for some subgroups, mainly for black participants. However, as the tests were applied using the whole cohort (n=13,245), we can assure that this problem was minimized. We also stated that the ethnoracial self-classification may be affected by both genome ancestry and non-biological factors.

With all that stated, and based on our findings, it is possible to conclude that the TG/HDL-C ratio is a robust and accurate marker for the prediction of cardiometabolic condi-

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tions, especially MetS. The sex- and ethnicity-specific reference values proposed in the present study were generated and tested on a large sample of Brazilian individuals, which is known as a mixed population. The use of the TG/HDL-C ratio in the clinical practice would help clinicians to early predict risk, and address proper care for individuals in the health system, potentially decreasing morbidity and mortality associated with the studied conditions.

Conflict of Interest

RDS has received honoraria related to consulting, speaker activities, or research from Abbott, Ache, Amgen, Astra Zeneca, Esperion, EMS, Getz pharma, Kowa, Libbs, Novo-Nordisk, Novartis, Merck, MSD, Pfizer, PTC Therapeutics, and Sanofi outside the present work. All other authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jacl.2021.07.005.

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