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Association Between Triglycerides, High-Density Lipoprotein Cholesterol, and Their Ratio With the Pulse Wave Velocity in Adults From the ELSA-Brasil Study

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Abstract

Atherogenic dyslipidemia is a risk factor for cardiovascular diseases. The present study aimed to evaluate the association between triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and the triglycerides to high-density lipoprotein (TG/HDL-C) ratio with carotid-femoral pulse wave velocity (cf-PWV), a marker of vascular stiffness. Anthropometric, biochemical, and clinical data from 13,732 adults were used to assess this association. Individuals within the third TG/HDL-C tertile presented worse anthropometric, biochemical, and clinical profiles as compared with the participants in the lower TG/HDL-C tertile. There was a linear association between TG, HDL-C, and TG/HDL-C ratio and cf-PWV in both men and women (stronger in women). After adjustment for confounders, lower levels of HDL-C were associated with increased cf-PWV in men (9.63 ± .02 m/s) and women (8.90 ± .03 m/s). However, TG was not significantly associated with cf-PWV after adjustment, regardless of sex. An increased TG/HDL-C ratio is associated with higher cf-PWV only in women (9.01 ± .03 m/s), but after adjustment for HDL-C levels, the association was non-significant (8.99 ± .03 m/s). These results highlight the stronger association of HDL-C with arterial stiffness, and that the association of TG/HDL-C with cf-PWV is dependent on HDL-C.

Keywords

arterial stiffness, triglycerides, high-density lipoprotein cholesterol, triglycerides/high-density lipoprotein cholesterol ratio

Introduction

Cardiovascular diseases (CVD) are a major public health problem, and a leading cause of death worldwide.[1] It is noteworthy that the majority of cardiovascular deaths are due to ischemic heart disease and stroke, which have atherosclerosis as a common underlying causal factor,[1] thus emphasizing the importance of vascular health.

Dyslipidemia is an important contributor to the atherosclerotic process, and is characterized by alterations in the serum levels of lipids, which may include increased total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein (VLDL-C), triglycerides (TG), and decreased high-density lipoprotein cholesterol (HDL-C).[2] Atherogenic dyslipidemia, characterized by an elevation in TG and reduction in HDL-C has gained special attention considering the epidemic of excess body weight and the control of LDL-C with statins as a cause of the so-called residual risk.[3]

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An imbalance in plasma lipids must be considered with great caution as they can interact with vessels, affecting vascular health by triggering several processes inside the artery wall.[4] In fact, evidence supports the association between serum lipid profile parameters and arterial stiffness,[5-7] a marker of vascular health, although controversial findings are still found.[8] Furthermore, arterial stiffness measured by the gold standard pulse wave velocity (PWV) method is considered a strong predictor of cardiovascular events,[9] mainly due to its potential to induce hypertension, left ventricle hypertrophy, impair coronary perfusion, and facilitate the formation and rupture of atherosclerotic plaques by inducing stress in the vascular wall.[10]

Serum TG, mainly found in chylomicrons (formed in the intestine after TG digestion and absorption) and VLDL-C (repackage of TG delivered to the liver by other lipoproteins) particles, are considered atherogenic when in contact with endothelial cells promoting the direct absorption of fatty acids, the release of inflammatory cytokines, and induction of apoptosis.[11] Metabolism of TG contributes to the formation of foam cells, which are classic components of the atheromatous plaque.[12] Moreover, when these particles are present at increased levels, they affect other lipid and lipoprotein structures and functions, such as transferring TG molecules to LDL-C and HDL-C particles.[13] Indeed, epidemiologic and genetic studies indicate that lower TG levels indicate better cardiovascular health.[13] In contrast, HDL-C levels are inversely associated with vascular disease, possibly due to its anti-atherogenic property, which is explained by this particle's main function of reverse cholesterol transport, along with its ability to activate anti-oxidant and anti-inflammatory pathways in endothelial, macrophages and smooth muscle cells.[11,14]

Therefore, increased TG and decreased HDL-C levels create a pro-atherogenic environment that is commonly associated with increased arterial stiffness. Also, the ratio between these two components—TG/HDL-C—can predict cardiometabolic risk in different populations.[15,16] However, it is still not clear if the TG/HDL-C ratio is independently associated with arterial stiffness. In this context, the present study aimed to evaluate the association of TG, HDL-C, and their ratio with arterial stiffness, by analyzing the Longitudinal Study of Adult Health (ELSA-Brasil), a large sample size study that consists of Brazilian adults.

Methods

Study Population

The ELSA-Brasil study is a prospective, multicenter cohort of 15,105 Brazilian adults, employed by six public universities or research institutions. Further details on the cohort may be found elsewhere.[17] The present study comprises a cross-sectional analysis of the ELSA-Brasil study cohort data.

The sample size for the ELSA-Brasil cohort was calculated based on its main study outcomes: type 2 diabetes and myocardial infarction. The estimated 3-year cumulative incidence of 1.4% was considered for diabetes. Considering an alpha value of 5%, statistical power of 80%, exposure prevalence of 20%, and a relative risk of 2.0, the estimated sample size was approximately 6400 subjects. This sample size would also allow for an adequate number of incident myocardial infarctions, as the estimated incidence of myocardial infarction, based on national mortality data, was expected to be slightly higher than that of diabetes. To present sex-specific analyses and allow for possible losses to follow-up, the desired sample size was approximately 15,000 persons.[18]

All participants provided their written informed consent, and the study was approved by the ethics committees of the institutions from where the participants were recruited. For the present study, we excluded those participants whose PWV measurements were not considered valid, those with previous self-reported cardiovascular diseases (myocardial infarction, stroke, rheumatic fever, cardiac surgery), those with fasting TG ≥500 mg/dL, HDL-C <25 mg/dL and >120 mg/dL, and with cf-PWV <3 m/s and >25 m/s. These limits were established based on the physiological plausibility of each parameter to avoid the influence of possible outliers in the analysis. Our final sample included 13,732 participants aged from 35 to 74 years.

Clinical Measurements

Anthropometric parameters (height, weight, and waist circumference (WC)) were obtained by using gold standard protocols and equipment, as previously described.[19] The body mass index (BMI) was calculated as the ratio between weight and the squared height (kg/m^2). For the biochemical analyses, blood samples were drawn from the participants after a fasting period of 10–14 h. The following parameters were assessed: TC, HDL-C, TG, LDL-C (assessed via Friedewald equation for TG <400 mg/dL, or measured by a direct method when TG ≥400 mg/dL), glucose, and uric acid levels. For the assessment of the estimated glomerular filtration rate (eGFR), urine samples were collected, and the Chronic Kidney Disease Epidemiology Collaboration formula was applied.[20] The Homeostasis Model Assessment for Insulin Resistance (HOMA-IR) was assessed with the following formula: (fasting glucose levels x fasting insulin levels)/405.[21] All the aforementioned analyses were performed in a central laboratory and the methods used are described elsewhere.[22,23]

The heart rate, systolic and diastolic blood pressures (SBP and DBP, respectively) were measured in the morning, after bladder emptying and a 5 min rest period, in the sitting position, with feet flat on the floor and back supported, using a validated oscillometric device (OMRON HEM 705CPINT, São Paulo, Brazil) in a temperature-controlled

room (20–24°C). With the middle of the cuff positioned on the patient's upper arm at the level of the right atrium (midpoint of the sternum), three measurements were performed (1 min intervals between each measurement), and the last two were used to determine clinical SBP and DBP. The cuff was chosen according to the participant's arm perimeter as instructed by the manufacturer.

Pulse Wave Velocity

The carotid-femoral pulse wave velocity (cf-PWV) was obtained by using a validated automatic device (Complior; Artech Medicale, Paris, France). The participants stayed in the supine position in a room with a controlled temperature set as 20–24°C. The arterial pressure was measured in the right arm with an oscillometric device (OMRON HEM 705CPINT, São Paulo, Brazil) to obtain a blood pressure-adjusted cf-PWV. Next, the pulse waveform was captured using a sensor positioned simultaneously in the carotid and femoral arteries, where the distance between the carotid-sternal notch to the right femoral site was measured with an inelastic metric tape. The pulse waveforms were visualized on a computer via specific software. The cf-PWV, expressed in m/s, was calculated by dividing the distance from the carotid-sternal notch to the right femoral site by the time delay between the carotid and the femoral pulse waves. Measurements obtained from 10 consecutive cardiac cycles were used for the average cf-PWV individual value definition.[22]

Statistical Analysis

All the statistical analyses were performed using SPSS software (version 22.0; SPSS, Inc, Chicago, IL, USA). Continuous variables are described as mean ± standard deviation, and categorical results were presented as frequency and percentage. We used the Kolmogorov-Smirnov test to evaluate the goodness-of-fit and the adequacy of a normal distribution. First, we used a one-way analysis of variance (ANOVA) followed by a Bonferroni *post hoc* test to assess the individual differences in some variables among tertiles of TG/HDL-C ratio. We next used univariate linear regression analyses to test the association between TG, HDL-C, and TG/HDL-C with cf-PWV. Analyses of covariance (ANCOVA) were applied to assess the association between cf-PWV and TG, HDL-C, and TG/HDL-C, and in addition to an unadjusted model, an adjusted model was tested with the following covariables included: age, BMI, uric acid levels, eGFR, SBP, and glucose levels. For all analyses, the statistical significance was set at a two-sided $P < .05$.

Results

The present study included 13,732 participants (54.8% were women). The general characteristics of the studied population are described in Table 1. Results from men were generally different from women regarding the clinical, biochemical, and hemodynamic profiles, presenting increased body weight, waist circumference, glucose levels, insulin resistance, SBP and DBP, and PWV. TG, TG/HDL-C, and uric acid levels were higher in men than in women. The HDL-C, on the other hand, was higher in women compared with men. Table 1 also presents the clinical, biochemical, and hemodynamic profiles stratified by tertiles of TG/HDL-C. In men, all variables, except age and height, were different across the TG/HDL-C ratio tertiles. In women, all variables were different across the TG/HDL-C ratio tertiles.

We then evaluated how TG, HDL-C, and TG/HDL-C varied with age (Figure 1). It was possible to observe that TG levels in men increased progressively with age up to 54 years old, and decreased in older individuals, while in women TG levels increased progressively up to 64 years old, entering a plateau afterward (Figure 1A), similarly to the TG/HDL-C ratio pattern (Figure 1C). HDL-C levels increased progressively with age in both men and women (Figure 1B).

We next examined the correlation between cf-PWV and the TG/HDL-C ratio and its components. We detected a positive significant correlation between cf-PWV and TG and TG/HDL-C for men (Figure 2A and G, respectively) and women (Figure 2B and H, respectively). Moreover, the slopes were steeper in women than in men (Figures 2C and I). The HDL-C levels displayed a positive significant correlation with cf-PWV in men (Figure 2D), while a negative correlation was observed for women (Figure 2E), and the slopes were statistically different in men compared with women (Figure 2F).

Finally, we tested whether the tertiles of TG, HDL-C, and TG/HDL-C ratio would associate with cf-PWV. We observed that in men and women, after adjustment for confounding variables (age, SBP, BMI, uric acid levels, eGFR, and glucose levels), TG was not associated with cf-PWV (Figure 3). Moreover, we detected a significant inverse association between HDL-C and cf-PWV, regardless of sex, showing that the higher the HDL-C levels, the lower the cf-PWV (Figure 3). When the association was tested for the TG/HDL-C ratio, it was significant only for women, but not for men (Figure 3). Finally, to test the significance of HDL-C on the association of TG/HDL-C with cf-PWV in women, we additionally adjusted the model for the HDL-C levels, and the association became non-significant (tertile 1: 8.94 ± 1.54; tertile 2: 9.00 ± 1.29; tertile 3: 9.00 ± 1.49; $P = .255$). It is noteworthy that, when the association was controlled by the TG levels, it remained significant. Also, possible differences attributed to race (black, brown, and white) were tested and displayed no significant interference (data not shown).

Table 1. Clinical and Anthropometrical Characteristics Stratified by Sex and TG/HDL-C Ratio Tertiles.

	Men					Women				
	Tertile 1 (n = 2060)	Tertile 2 (n = 2081)	Tertile 3 (n = 2065)	*P*	All (n = 6206)	Tertile 1 (n = 2479)	Tertile 2 (n = 2545)	Tertile 3 (n = 2502)	*P*	All (n = 7526)
Age (years)	51.6 ± 9.6	51.6 ± 9.2	51.8 ± 8.6	.674	51.7 ± 9.1	50.4 ± 8.8	51.8 ± 8.8[a]	53.1± 8.6[a b]	<.001	51.8 ± 8.8
Height (cm)	172.3 ± 7.3	172.2 ± 6.7	171.9 ±7.0	.203	172.1 ± 7.1	159.4 ± 6.5	159.1 ± 6.5	158.7 ± 6.5[a]	.003	159.1 ± 6.5
Weight (Kg)	74.7 ± 13.2	80.4 ± 13.9[a]	83.6 ± 13.7[a b]	<.001	79.6 ± 14.1	63.4 ± 11.6	68.5 ± 13.3[a]	72.6 ± 13.7[a b]	<.001	68.2 ± 13.4
BMI (Kg/m^2)	25.1 ± 3.9	27.1 ± 4.1[a]	28.2 ± 3.9[a b]	<.001	26.8 ± 4.2	24.9 ± 4.3	27.0 ± 4.9[a]	28.8 ± 4.9[a b]	<.001	26.9 ± 5.0
WC (cm)	89.6 ± 11.0	95.8 ± 11.3[a]	99.0 ± 10.2[a b]	<.001	94.8 ± 11.5	81.5 ± 10.7	87.7 ± 11.9[a]	92.9 ± 11.7[a b]	<.001	87.4 ± 12.4
Glucose (mg/dL)	109 ± 24	114 ± 29[a]	122 ± 38.1[a b]	<.001	115 ± 31	101 ± 17	106 ± 21[a]	115 ± 35[a b]	<0.001	107 ± 26
Insulin (μIU/mL)	9.1 ± 5.7	12.5 ± 10.4[a]	15.8 ± 11.2[a b]	<.001	12.4 ± 9.8	8.4 ± 6.9	11.0 ± 7.4[a]	14.7 ± 10.3[a b]	<.001	11.4 ± 8.7
HOMA-IR	2.4 ± 2.0	3.5 ± 4.4[a]	4.7 ± 5.2[a b]	<.001	3.5 ± 4.2	2.1 ± 2.7	2.8 ± 2.1[a]	4.0 ± 3.5[a b]	<.001	3.0 ± 2.9
TC (mg/dL)	203 ± 38	213 ± 40[a]	222 ± 42[a b]	<.001	212 ± 41	208 ± 37	215 ± 39[a]	226 ± 43[a b]	<.001	216 ± 40
LDL-C (mg/dL)	127 ± 32	137 ± 34[a]	132 ± 37[a b]	<.001	132 ± 35	123 ± 31	134 ± 33[a]	138 ± 37[a b]	<.001	131 ± 34
HDL-C (mg/dL)	60 ± 13	49 ± 8[a]	44 ± 7[a b]	<.001	51 ± 12	72 ± 14	61 ± 11[a]	52 ± 10[a b]	<.001	62 ± 14
TG (mg/dL)	82 ± 22	132 ± 28[a]	238 ± 74[a b]	<.001	150 ± 80	67 ± 178	105 ± 22[a]	180 ± 62[a b]	<.001	117 ± 61
TG/HDL-C ratio	1.4 ± 0.4	2.7 ± 0.4[a]	5.5 ± 1.8[a b]	<.001	3.2 ± 2.0	1.0 ± 0.2	1.7 ± 0.3[a]	3.5 ± 1.4[a b]	<.001	2.1 ± 1.4
Uric Acid (mg/dL)	5.9 ± 1.2	6.4 ± 1.3[a]	6.9 ± 1.4[a b]	<.001	6.4 ± 1.4	4.3 ± 1.0	4.7 ± 1.1[a]	5.3 ± 1.2[a b]	<.001	4.8 ± 1.2
eGFR (mL/min/1.73 m^2)	83 ± 14	82 ± 15[a]	81 ± 15[a b]	<.001	82 ± 15	103 ± 12	101 ± 12[a]	100 ± 13[a b]	<.001	101 ± 12
SBP (mmHg)	123 ± 17	124 ± 16[a]	127 ± 16[a b]	<.001	125 ± 17	114 ± 15	117 ± 16[a]	121 ± 17[a b]	<.001	117 ± 17
DBP (mmHg)	77 ± 11	78 ± 10[a]	81 ± 10[a b]	<.001	79 ± 11	72 ± 10	74 ± 10[a]	76 ± 10[a b]	<.001	74 ± 10
HR (bpm)	68 ± 11	69 ± 10[a]	71 ± 10[a b]	<.001	69 ± 11	71 ± 10	71 ± 10	71 ± 10[a]	.022	71 ± 10
cf-PWV (m/s)	9.5 ± 1.8	9.6 ± 1.8	9.9 ± 1.8[a b]	<.001	9.7 ± 1.8	8.6 ± 1.5	9.0 ± 1.7[a]	9.3 ± 1.8[a b]	<.001	9.0 ± 1.7

Abbreviations: BMI, Body mass index; WC, Waist circumference; HOMA-IR, Homeostasis model assessment of insulin resistance; TC, Total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; TG/HDL-C, triglycerides/high-density lipoprotein cholesterol ratio; eGFR, Estimated glomerular filtration rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; cf-PWV, carotid-femoral pulse wave velocity.

[a] vs T1.

[b] vs T2 (One-way ANOVA).

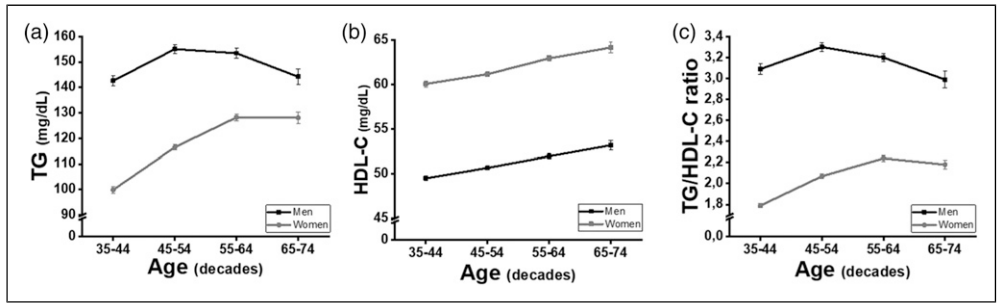

Figure 1. Lipid levels by age categories and sex. (a) Triglycerides (mg/dL); (b) High-density lipoprotein cholesterol (mg/dL); and (c) Triglycerides/high-density lipoprotein cholesterol ratio. One-way ANOVA: two-tailed $P < .0001$ for men and women for all factors. TG: triglycerides; HDL-C: high-density lipoprotein cholesterol; TG/HDL-C: triglyceride/high-density lipoprotein cholesterol ratio. Data represent the mean and standard error.

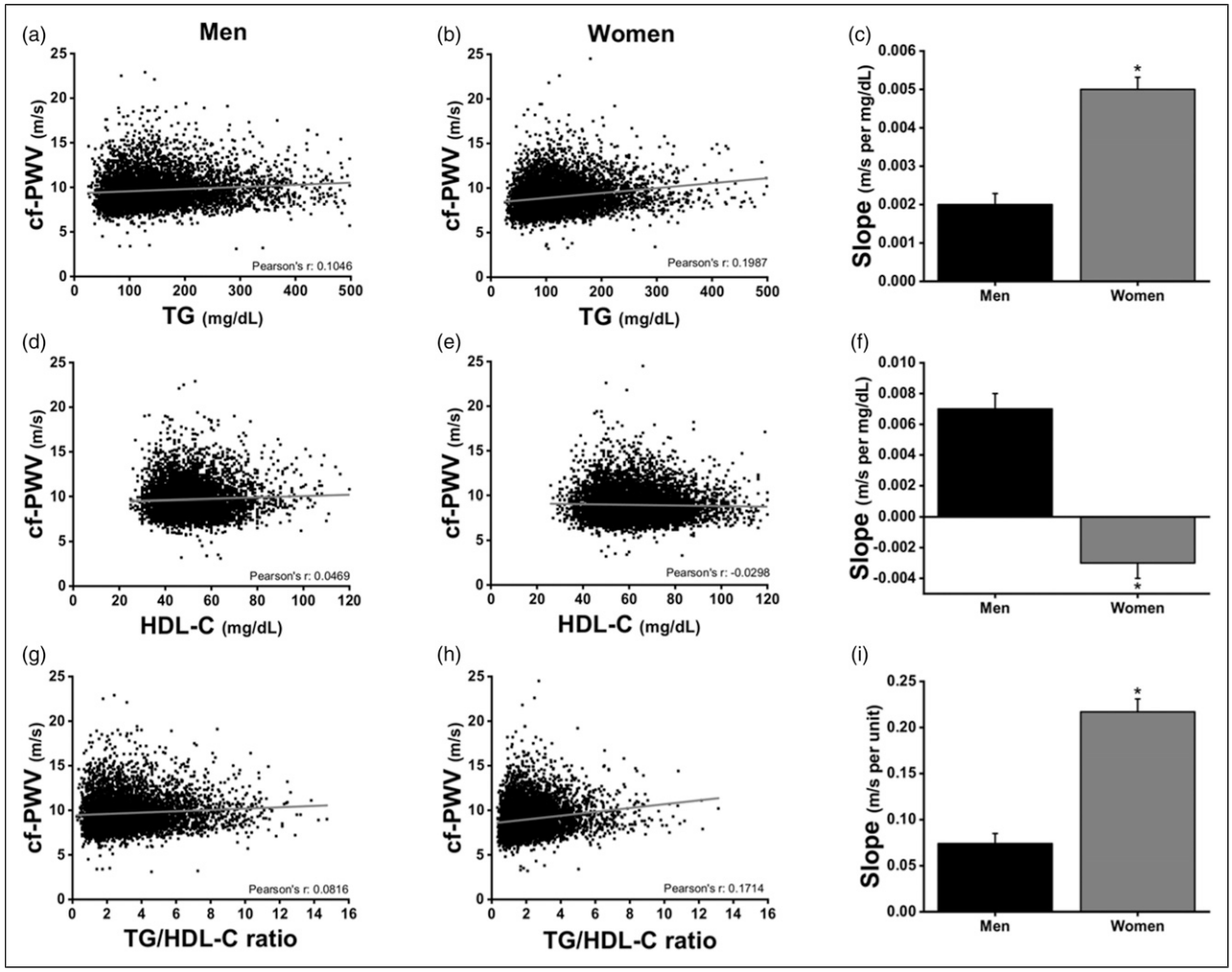

Figure 2. Linear regression between carotid-femoral pulse wave velocity (cf-PWV) and triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) and triglycerides/high-density lipoprotein cholesterol ratio (TG/HDL-C) in men (a,d, and g, respectively) and women (b,e, and h, respectively) and the comparison between the slope of increase in cf-PWV according to the levels of TG, HDL-C, and TG/HDL-C ratio in men and women (c,f, and i, respectively). Data represent the mean and standard error.

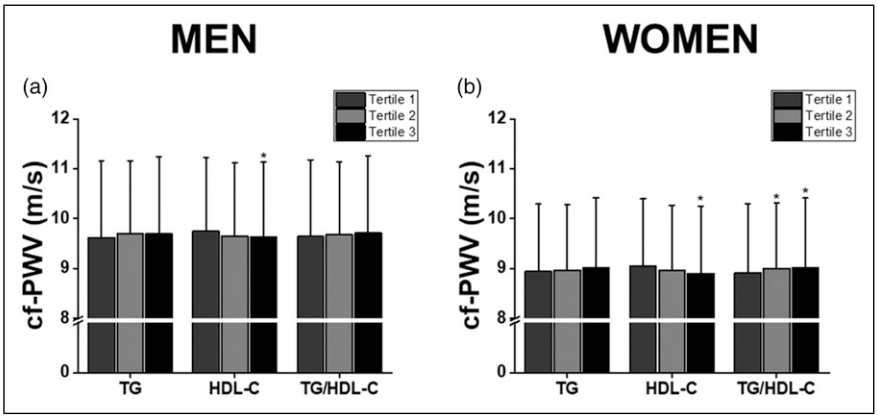

Figure 3. Variations in carotid-femoral pulse wave velocity (cf-PWV) in men (a) and women (b) according to triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) and triglycerides/high-density lipoprotein cholesterol ratio (TG/HDL-C) levels stratified by tertiles. *$P <$ .05. Values adjusted by age, BMI, SBP, uric acid levels, GFR, and glucose levels. Data represent the mean and standard deviation.

Discussion

In the present study, HDL-C levels, but not TG levels, were associated with increased cf-PWV in men and women. The TG/HDL-C ratio was also associated with higher cf-PWV, but only in women. This was mostly attributed to the contribution of HDL-C. These findings highlight the relation of HDL-C with the vascular wall.

The association between TG and arterial stiffness is controversial. Wang et al[24] showed in a community-based prospective study that TG was a predictive factor for arterial stiffness, assessed by cf-PWV. The authors showed that lower TG levels were associated with a reduction in cf-PWV, supporting TG-lowering therapies.[24] These data were corroborated in apparently healthy individuals in a cross-sectional study that associated TG levels and the augmentation index, a composite measure of arterial stiffness and wave reflection.[25] This association was also confirmed by others.[7,26] Other studies, however, failed to report an association between TG and cf-PWV,[5,6] including a systematic review that included 38 studies,[27] corroborating our findings.

The literature provides a possible explanation for the controversial association of TG with PWV. The effects of TG on the vascular wall may require a latency period to significantly influence wall elasticity, while other parameters, such as inflammation, exert more persistent effects, thus being more easily associated.[7] Finally, the literature supports the hypothesis that TG may exert its effects through its influence on HDL-C particle size.[28] Increased TG levels are commonly accompanied by increased transfer of TG to HDL-C mediated by cholesteryl ester transfer protein (CETP).[29] In turn, HDL-C enrichment with TG may lower HDL-C circulating levels[30] and impair HDL function.[31]

Unlike for TG, our findings showed that HDL-C is inversely associated with cf-PWV in men and women, even after adjustment for confounding factors. It was previously shown that low HDL-C levels are associated with increased carotid intima-media thickness.[32] Low HDL-C levels are also indirectly associated with oxidative products that are linked to inflammation and cell stress,[33] considered triggering factors for arterial stiffening. The negative association between HDL-C and cf-PWV is explained by this particle's anti-atherogenic, anti-inflammatory, anti-thrombotic, and anti-oxidative properties, which are necessary for vascular homeostasis.[34] Interestingly, it seems that the anti-inflammatory properties of HDL mediate its association with cf-PWV, as shown in a study where the correlation between HDL-C and cf-PWV was attenuated by increases in high-sensitivity C-reactive protein (hsCRP) levels, a well-established inflammatory marker.[14] Additionally, HDL-C is responsible for reverse cholesterol transport, which is necessary for vascular wall health.[34]

Several studies support the association between HDL-C and PWV.[6,34,35] Havlik et al evaluated the association between several risk factors and PWV, and after multiple regression models, only age and HDL-C remained significant, the latter displaying a negative association with PWV. The authors pointed out that HDL-C seems to be an indicator, although indirectly, of aerobic capacity or less atherosclerosis.[36] Similarly, Lebrun et al[37] in a study performed with postmenopausal women reported negative associations between HDL-C and PWV, also highlighting the increased risk of stroke, death, and coronary artery disease as PVW increases. Tsioufis et al[38] investigated the impact of metabolic syndrome on cardiovascular markers in individuals with essential hypertension and reported a statistically significant association between low HDL-C levels and cf-PWV. HDL-C levels were also negatively associated with PWV and left ventricular diastolic function in a study involving untreated hypertensive men and women, even after adjustments.[39] Roes et al[35] corroborated these data in a small study, reporting an independent negative association between HDL-C, aortic PWV, and left ventricular diastolic function, both assessed via magnetic resonance imaging, emphasizing this lipid particle cardioprotective

properties. Other studies, however, failed to demonstrate a significant association between HDL-C and PWV. Beneros et al[40] reported no association between HDL-C and baseline PWV or PWV progression, the last measured on a 5-year follow-up. Dart et al[41] also corroborated the lack of association between HDL-C and PWV, justified by the possible increased use of lipid-lowering medications that would have impacted the cholesterol levels of the study participants. Alvim et al,[42] in a random sample of Brazilian adults, reported discordant associations between HDL-C and PWV in men and women, where a statistically significant association was only found in postmenopausal women, which might be linked to the estrogen influence on lipid metabolism.

It has been proposed, however, that lipid ratios are also reliable risk predictors.[43] The TG/HDL-C ratio is being studied to detect and predict the risk of several cardiometabolic alterations, including metabolic syndrome, insulin resistance, hypertension, diabetes, and cardiovascular diseases.[15] This ratio displayed the ability to stratify individuals with similar diagnoses (e.g., hypertension) but different cardiometabolic risks,[44] or to detect "healthy" individuals with unknown insulin resistance and consequently increased cardiometabolic risk.[16] The TG/HDL-C is associated with insulin resistance, as proposed by McLaughlin et al who originally introduced this ratio,[45] explains, at least in part, its impact on vascular health. Insulin resistance is a common feature of cardiometabolic conditions such as obesity, diabetes, and hypertension, and is known to induce endothelial dysfunction, oxidative stress, and inflammation.[46] All of these factors are associated with atherosclerosis and, consequently, with arterial wall dysfunction.

In this context, a major finding of the present study was the significant association between TG/HDL-C and cf-PWV in women. Others attempted to evaluate the association between TG/HDL-C and cf-PWV in different study designs. Vallée et al[47] evaluated the association between several lipid parameters and aortic stiffness in 603 French participants, reporting an association with non-HDL-C, TC, and TC/HDL-C, while no association with TG/HDL-C was reported. Chen et al, in a study performed with Japanese men and women, reported no association between TG/HDL-C and brachial-ankle PWV (baPWV) after adjustments for several confounding factors, which was explained by a non-linear relationship observed between these parameters.[48] In contrast, a study involving 2278 apparently healthy Chinese individuals showed an independent association between TG/HDL-C with altered baPWV.[49] However, they used baPWV, which is different from the parameter used in the present study, although it is also used to detect arterial stiffness.[50] Wen et al also evaluated several lipid parameters and their ratios in 1015 young Chinese men and reported that lipid ratios are superior to conventional lipid parameters for predicting this vascular dysfunction and that TG/HDL-C showed the strongest association,[51] this was corroborated in apparently healthy adolescents and young adults.[52] Interestingly, Shimizu et al[53] reported diabetes accompanied by high TG/HDL-C to constitute a significantly increased risk for arterial stiffness and atherosclerosis, highlighting the interplay between cardiovascular and metabolic risk factors. In our findings, the association of TG/HDL-C with cf-PWV observed in women seems to depend on the HDL-C, thus not being considered an independent association. This result highlights the important role of HDL-C on vascular health.

As reported above, our findings corroborate previous studies, by confirming the association between TG/HDL-C and arterial stiffness. However, in the present study, it was possible to observe that the association between TG/HDL-C ratio with arterial stiffness differed in men and women after the adjusted analyses. This difference remains to be clarified, as variations in height, and consequently decreased distances between the heart and reflecting sites are not sufficient to explain the discordant results reported in our study for men and women.

An interesting finding of our study, however, may explain, at least in part this sex difference observed. In the present study, a positive linear association between HDL-C and cf-PWV was observed in men, while a negative association was found in women. This might be explained by sex differences in the lipid sub-particles. Women may have higher levels of atheroprotective HDL sub-particles when compared with men.[54] These findings, although still controversial, support the stronger significance of HDL-C on the TG/HDL-C association with cf-PWV in women. It seems reasonable to believe that decreases in the HDL-C levels in women may be more deleterious to vascular health as compared with men.

There is evidence that estrogen signaling has a positive influence on cholesterol efflux capacity, mainly via HDL activity.[55] Moreover, estrogen is associated with increased HDL-C levels through possible mechanisms, including estrogen-mediated increased VLDL metabolism that leads to increased HDL formation, estrogen-induced apoA-I synthesis in the liver, and estrogen inhibitory effect on hepatic lipase activity.[56] Altogether, these pathways may partially explain the discordant association observed between HDL-C and cf-PWV in men and women observed in the present study. However, further studies aiming to investigate differences in arterial structure or function that affect the pulse wave behavior are needed, emphasizing the importance of performing sex-specific analyses, as already supported by others.[57]

Finally, it is important to argue that several factors increase arterial stiffness; aging and increased SBP are the most important contributors.[22] We have evaluated the association of cf-PWV and age, but extrapolate this analysis by progressively excluding risk factors from the entire sample, showing that the exclusion of risk factors (hypertension, prehypertension, diabetes, overweight/obesity, and smoking) causes a progressive reduction in the rate of increase in cf-PWV with age.[22] These findings highlight that although risk factors other than age and SBP exert a smaller effect on cf-PWV, when combined, their effect on the arterial wall may become significantly harmful.

In this sense, the relatively small association between the lipid parameters and the cf-PWV observed in the present study must be viewed in a greater context and as a contributor to arterial wall injury, along with other factors that may determine greater cardiovascular risk.

This study has some limitations. The cross-sectional design does not allow causal relationships; reverse causation cannot be excluded. Also, we have used stratifications (sex and tertiles of lipid parameters) that reduce the sample size in each group. However, given the large sample size of the ELSA-Brasil study, the power of the analyses was satisfactory.

In conclusion, our findings demonstrate the stronger association of HDL-C with arterial stiffness, while TG seems to have no association with this parameter. Moreover, the TG/HDL-C association with arterial stiffness observed in women was shown to be dependent on the HDL-C variance. These findings highlight the link between lipid markers and arterial stiffness, but although the TG/HDL-C ratio can be safely used to identify people at cardiometabolic risk,[15] it probably should not be used to predict the risk of arterial stiffening.

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Author Contributions

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Declaration of Conflicting Interests

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