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Association of obesity and LDL subfractions evaluated by body mass index, waist circumference, and diabetes status: the ELSA-Brasil study

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Abstract

Low-density lipoproteins (LDL) comprise a pool of particles with different densities that may have variable impact on atherogenesis. Studies suggest that obese individuals with elevated body mass index (BMI) and waist circumference (WC) have increased small and dense LDL subfractions (sdLDL-c). It is unclear if diabetes (T2D) and insulin resistance (IR) may modify this association. We included 4,111 (50.4 ± 8.6 years of age, 45.5% men) individuals with neither prior cardiovascular disease nor use of lipid-lowering medications. Total LDL-c and its subfractions (LDL_1-c, LDL_2-c, LDL_3-c, and LDL_4-c) were measured by vertical zonal ultracentrifugation. We considered the subfractions LDL_1-c and LDL_2-c as large buoyant LDL (lbLDL-c) and the subfractions LDL_3-c and LDL_4-c as sdLDL-c. We analyzed the association between LDL-c subclasses, BMI and WC using linear regression analysis and stratified by the presence of T2D and IR. For sdLDL-c, a direct association with hypertension, T2D, fasting plasma glucose, total cholesterol, LDL-c, and triglycerides was observed. In multivariate analysis, after adjustment for age, sex, race and triglycerides, the strong association of sdLDL-c with BMI (β 95% CI 0.16 (0,13–0,19)) and WC (β 95% CI 0.22 (0.19–0.26)) persisted. After stratification, the association of sdLDL-c and WC was present only in those with insulin resistance or diabetes. BMI showed a smaller impact than WC on this association. WC and BMI were strongly associated with sdLDL-c subfractions. Further, this association was modified by diabetes and insulin resistance status.

Keywords Low-density lipoprotein subclasses, Obesity, Body mass index, Waist circumference

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Introduction

Obesity, defined as an excess of body fat and commonly measured by BMI, is a prevalent condition worldwide. It is linked to increased cardiovascular disease risk, mainly due to its comorbidities, such as hypertension, insulin resistance, type 2 diabetes (T2D), and dyslipidemia [1, 2]. In this setting, the elevated triglycerides (TG) levels (including remnant cholesterol) [3], low high-density lipoprotein (HDL) and predominance of the small and dense low lipoprotein (sdLDL) distribution pattern characterize the so-called atherogenic lipid triad [4, 5].

It is well-known that obesity is linked to a worse clinical profile, as many epidemiological studies have demonstrated a strong association of indices of obesity, such as visceral adipose tissue [6], subcutaneous adipose tissue (SAT), WC and BMI, with coronary heart disease (CHD) and its risk factors [7–9]. Also, evidence suggests that WC, which reflects abdominal adiposity, is a superior predictor of all cause and cardiovascular mortality and CVD outcomes [10], even after adjusted for BMI [11] in some analyses. Further, obesity is still related to increased sdLDL particle levels [12] while abdominal fat volume measured by computed tomography (CT) scanning is positively associated with sdLDL-c but inversely associated with large buoyant LDL-c (lbLDL-c) [13].

The sdLDL-c levels are also elevated in diabetic dyslipidemia, leading to increased CVD risk in this population [14, 15]. It is also known that this association is related to BMI and WC, with the latter being a better predictor [16]. Due to known metabolic pathways involving lipoprotein lipase inhibition, increased hepatic lipase activity on HDL and LDL, T2D and IR play an important role in the potential lipid profile changes in obese individuals [4, 5, 17].

Therefore, in the present study we aimed to analyze the association between LDL-c subfractions and obesity assessed by BMI and WC and how this could be modified by the presence or absence of T2D and IR in a multiethnic Brazilian cohort.

Methods

Sample. Between August 2008 and December 2010, 15.015 men and women were enrolled in the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), a prospective longitudinal cohort composed of civil servants aged 35 to 74 years from six Brazilian cities. Details about the cohort were previously published [18, 19]. We included all participants from the São Paulo center ($n = 5{,}061$) who underwent LDL-c measurement using the vertical auto profile (VAP) method. Exclusion criteria for the present analysis were the lack of serum measurement of any component of the lipid profile, previous history of cardiovascular disease (myocardial infarction, stroke, heart failure and coronary revascularization), and participants using any lipid lowering drug at baseline. After applying these exclusion criteria, the total sample size was $n = 4{,}111$.

Race. Race was defined in a self-declared answer according to the terms used in the IBGE (Instituto Brasileiro de Geografia e Estatistica) census "black", "brown", "white", "yellow" and "indigenous".

LDL-c and subfractions analysis. After blood collection during nocturnal fasting, the samples were centrifuged at the sites and stored in tubes at − 80 °C. LDL-c and its subfractions LDL_1-c, LDL_2-c, LDL_3-c and LDL_4-c were measured by the VAP method (Atherotech®), a gradient ultracentrifugation (UC) method with inverted rate zonal, single vertical spin, that simultaneously measures cholesterol concentrations after fraction separation and has a close correlation to the conventional method [20]. After the UC step, cholesterol of each subfraction was measured by enzymatic methods. We considered the subfractions LDL_1-c and LDL_2-c as large buoyant LDL (lbLDL-c) and the subfractions LDL_3-c and LDL_4-c as small and dense LDL-c (sdLDL-c). In addition, we also used the sdLDL-c/ total LDL-c ratio, as a log-transformed variable due to its normal distribution. It represents the amount of sdLDL-c in LDL-c.

Hypertension. Defined as systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg or verified treatment with anti-hypertensive medication during the last 2 weeks.

Diabetes. T2D diagnosis was defined as a reported history of diabetes mellitus, insulin use or any oral antidiabetic drugs. Also, l laboratory criteria included fasting plasma glucose ≥ 126 mg/dl; HbA1c levels ≥ 6.5% or a 2-hour oral glucose tolerance test ≥ 200 mg/dl.

Insulin resistance. The homeostasis model assessment-estimated insulin resistance (HOMA-IR) value was obtained by fasting blood glucose X 0.0555 X fast blood insulin/22.5 [21].

Hypercholesterolemia. Hypercholesterolemia was defined as a low-density lipoprotein cholesterol (LDL-C) level ≥ 130 mg/dL.

Obesity measurements

Body Mass Index: based on measured height and weight obtained on ELSA-Brasil, calculated by dividing the weight by the square of the height.

Waist circumference: WC was measured with a measuring tape equidistant from the lower margin of the rib and the iliac crest [22].

Other variables

Smoking. Participants were classified as never smokers, current smokers, and former smokers, for those who stopped smoking, but his/her tobacco exposure was more than 100 cigarettes throughout life.

Statistical analysis

Continuous variables are presented as mean and standard deviation (± SD) if normally distributed or as median (interquartile range, IQR) if non-normal distributed, while categorical variables were presented as absolute and relative frequencies. Data are displayed by four BMI strata (< 18.5; 18.5–25; 25–30 and > 30 kg/m^2), sdLDL-c upper (above p50 = 53.4) and lower (below p50 = 53.4) than the 50th percentile and lbLDL-c upper (above p50 = 41.2) and lower (below p50 = 41.2) the 50th percentile.

We performed comparisons of quantitative variables across groups using analysis of variance [23] or Kruskal-Wallis test according to their distributions. Categorical variables were analyzed by the Chi square test ($\chi 2$). As a correlation measurement, we used the Spearman test in bivariate analysis and, to assess the association between LDL-C subfractions and other variables, we constructed bivariate and multivariate linear regression models. For these models, we standardized LDL-C, LDL_1-c, LDL_2-c, LDL_3-c, LDL_4-c, and LDL-c log ratio. Multiple linear regression models were adjusted for race, sex, age, and triglycerides. Further, we constructed a sensitivity analysis stratifying by T2D status and IR.

Statistical significance was defined as $p < 0.05$. All analyses were performed with Stata version 14.0 (StataCorp, USA).

Results

We included 4,111 participants with a mean age of 50.4 (± 8.6) years-old, and 1,871 (45%) were males. As expected, we observed a positive association between higher BMI and WC, triglycerides, systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting glucose, LDL-C and total cholesterol and hypertension, while there was an inverse association between BMI and HDL-c (Table 1).

For sdLDL-c, we observed a worse profile for all traditional risk factors for cardiovascular disease, including SBP, DBP, T2D, fasting plasma glucose, total cholesterol,

Table 1 Baseline demographic characteristics of the studied sample

Clinical Profile	*n* = 4,111	Body Mass Index (BMI)				
Mean (± SD) or *n* (%)	**Total**	**< 18.5**	**18.5–25**	**25–30**	**> 30**	***P* Value**
Age (years)	50.4 (± 8.6)	48.8 (± 8.7)	49.98 (± 8.7)	50.7 (± 8.5)	50.57 (± 8.5)	0.0473
Male (n, %)	1871 (45.5)	20 (51.2)	639 (43.1)	835 (50.8)	377 (39.8)	< 0.0001
Race (n, %)						
White	2,382 (57.9)	29 (74.3)	905 (61.0)	944 (57.4)	504 (53.2)	
Black	580 (14.1)	2 (5.1)	165 (11.1)	237 (14.4)	176 (18.5)	
Brown	897 (21.8)	4 (10.2)	292 (19.7)	371 (22.5)	230 (24.2)	
Other	203 (4.9)	4 (10.2)	106 (7.1)	68 (4.1)	25 (2.6)	
Hypertension (n, %)	1,099 (26.75)	2 (5.13)	249 (16.80)	469 (28.55)	379 (40.11)	
SBP (mmHg)	119.1 (± 16.48)	111.9 (± 16.7)	115.1 (± 15.8)	120.2 (± 16.07)	123.7 (± 16.2)	
DBP (mmHg)	75.1 (± 10.8)	69.89 (± 11.7)	71.8 (± 10.4)	75.4 (± 10.0)	80.0 (± 10.6)	
T2D (%)	688 (16.7)	4 (10.2)	143 (9.6)	261 (15.9)	280 (29.5)	
FPG (mg/dL)	109.5 (± 27.4)	100.2 (± 8.0)	104.0 (± 18.9)	109.4 (± 25.0)	118.9 (± 38.4)	
HbA1c (%)	5.42 (± 0.91)	5.39 (± 0.56)	5.30 (± 0.73)	5.39 (± 0.87)	5.68 (± 1.17)	
Smoking (n, %)						
Current	687 (16.7)	14 (35.9)	290 (19.6)	268 (16.3)	115 (12.1)	
Former	1215 (29.5)	3 (7.7)	364 (24.5)	549 (33.4)	299 (31.5)	
Total Cholesterol (mg/dL)	215.0 (± 41.7)	194.6(± 33.3)	210.7 (± 40.0)	216.8 (± 40.3)	219.5 (± 45.9)	
LDL-c (mg/dL)	132.40(± 34)	112.2 (± 24.1)	128.7 (± 32.7)	134.5 (± 33.9)	135.3 (± 36.5)	
HDL-c (mg/dL)	56.44 (± 14.55)	64.82 (± 16.71)	60.16 (± 15.30)	55.03 (± 14.10)	52.74 (± 12.45)	
Triglycerides (mg/dl)	110 (79–159)	84 (65–105)	92 (69–127)	117 (84–169)	136 (99–183)	
LDL1-c (mg/dL)	22.6 (± 9.5)	20.5 (± 8.9)	22.3 (± 9.8)	22.8 (± 9.4)	22.7 (± 9.1)	0.2266
LDL2-c (mg/dL)	32.8 (± 17.9)	36.5 (± 12.60)	35.4 (± 17.2)	31.6 (± 18.1)	30.7 (± 18.3)	< 0.0001
LDL3-c(mg/dL)	47.1 (± 20.2)	33.8 (± 12.6)	43.6 (± 19.6)	48.7 (± 20.1)	50.3 (± 20.6)	
LDL4-c(mg/dL)	10.4 (± 12.1)	5.3 (± 5.1)	8.7 (± 9.1)	11.3 (± 11.1)	11.98 (± 12.1)	
lbLDL-c (mg/dL)	55.4 (± 24.1)	57.0 (± 18.9)	57.76 (± 23.8)	54.41 (± 24.2)	53.4 (± 24.2)	
sdLDL-c (mg/dL)	57.6 (± 26.6)	39.1 (± 14.3)	52.3 (± 25.2)	60.0 (± 26.8)	62.3 (± 27.1)	
WC []	89.26 (± 12.4)	67.8 (± 6.0)	78.8 (± 7.1)	90.6 (7.1)	104.08 (± 9.7)	

SD: standard deviation; % percentage; BMI: body mass index; FPG: fasting plasma glucose; SBP: systolic blood pressure; DBP: diastolic blood pressure; HbA1C: glycated hemoglobin WC: waist circumference; lbLDL-c: large buoyant low-density lipoprotein-cholesterol; sdLDL-c: small dense low-density lipoprotein-cholesterol. Total cholesterol, LDL-c, HDL-c, and TG were determined by conventional analysis (not VAP)

Table 2 Sample characteristics according to small dense LDL-c percentiles

Clinical Profile	Small-dense LDL-c		*P*-value
	p < 50th	*p* ≥ 50th	
Age (years)	50.0 (± 8.6)	50.8 (± 8.5)	< 0.0001
Male (%)	663 (32.5)	1208 (58.2)	
Race			0.104
White (%)	1197 (59.4)	1185 (57.9)	
Black (%)	302 (15.0)	278 (13.6)	
Brown (%)	431 (21.4)	466 (22.8)	
Others (%)	85 (4.2)	118 (5.7)	
Total Cholesterol (mg/dL)	199.5 (± 38.4)	230.3 (± 39.1)	0.0025
LDL-c(mg/dL)	117.6 (± 28.7)	147.5 (± 32.5)	< 0.0001
HDL-c (mg/dL)	61.1 (± 15.3)	51.9 (± 12.1)	
Triglycerides (mg/dl)	88 (67–119)	140 (102–192)	
T2D (%)	272 (13.35)	416 (20.07)	
FPG (mg/dL)	105.5 (± 21.0)	113.5 (± 32.0)	
HbA1c (%)	5.37 (± 0.83)	5.47 (± 0.98)	0.0006
Hypertension (%)	449 (22.0)	650 (31.3)	< 0.0001
SBP (mmHg)	116.6 (± 16.3)	121.6 (± 16.1)	
DBP (mmHg)	73.3 (± 10.6)	76.89 (± 10.6)	
Smoking			
Current (%)	309 (15.2)	378 (18.2)	
Former (%)	566 (27.8)	649 (31.3)	
WC	85.92 (± 12.42)	92.54 (± 11.60)	

SD: standard deviation; % percentage; BMI: body mass index; DLP: Dyslipidemia; SBP: systolic blood pressure; DBP: diastolic blood pressure; glucose: fasting glucose; HbA1C: glycated hemoglobin WC: waist circumference. Total cholesterol, LDL-c, HDL-c, and TG were determined by conventional analysis (not VAP)

Table 3 Univariate and multivariate linear regression for the association of LDL-c, LbLDL, SdLDL and LDL-c log ratio with BMI and WC

	BMI		WC	
Lipid profile (per 1SD)	Bivariate β (95% CI)	Multivariate	Bivariate β (95% CI)	Multivariate
LDL-c (mg/dl)	0.08 (0.05; 0.11)	0.06 (0.03; 0.09)	0.12 (0.09; 0.15)	0.09 (0.05 -; 0.12)
lbLDL-c (mg/dl)	0.03 (0.004; 0.064)	0.001 (− 0.02; 0.03)	0.0006 (-0.03; 0.03)	0.03 (-0.03; 0.03)
sdLDL-c (mg/dl)	0.15 (0.12; 0.18)	0.05 (0.02; 0.08)	0.28 (0.25; 0.31)	0.09 (0.06; 0.12)
LDL-c log ratio (sdLDL-c/LDL-c)	0.088 (0.05; 0.11)	0.04 (0.01; 0.07)	0.20 (0.17; 0.23)	0.07 (0.04; 0.10)

LDL -C: LDL cholesterol; lbLDL: large buoyant LDL subfractions; sdLDL: small and dense LDL subfractions. The multivariate analyses were adjusted for sex, age, race, and triglycerides

LDL-c, triglycerides, and hypertension, in individuals above the 50th percentile for sdLDL-c (p50 = 53.4). Also, there was an association between male sex and lower HDL-C levels (Table 2). These findings contrasted with the large buoyant LDL (lbLDL-c), where values above the 50th percentile were associated with a lower prevalence of traditional risk factors and higher HDL-C levels. Additionally, individuals with higher levels of lbLDL-c were more likely to be females (S1). For lbLDL-c we found an inverse association with both BMI and WC whereas the opposite was found concerning sdLDL-c.

When evaluating each LDL-C subfraction, we noted that LDL_2-c level decreases as BMI increases, while the LDL_1-c concentration was similar across BMI groups. The LDL_2-c levels drove the overall inverse association between lbLDL-c and BMI. On the other hand, both LDL_3-c and LDL_4-c increase as BMI rises.

In the linear regression models, we observe a strong correlation of LDL-c with BMI and WC. For sdLDL-c, the association with BMI and WC was also strong, but not between lbLDL-c and BMI or WC (Table 3; Figs. 1 and 2). Also, there was a robust association of the LDL-c log ratio with BMI and WC. In multivariate analysis, these findings were consistent even after adjustment for age, sex, race, and triglycerides. (Table 3; Figs. 1 and 2).

Further, we observed that the T2D modifies the association between sdLDL-c and both WC and BMI (Fig. 3C and D), since this association was especially stronger in non-T2D diabetes even after adjustment for age, sex, race, and triglycerides (S2). For the lbLDL-c interaction was positive with WC but negative with BMI. We also constructed multiple regression models stratified by IR ($p < 50$th and $p \geq 50$th) that corroborated the findings. (tables S3 and S4).

Discussion

The main findings of this cross-sectional study were that WC and BMI were strongly associated with small and dense LDL-c subfractions, but only weakly associated with large buoyant LDL-c subfractions. After stratification for T2D, the association of the sdLDL-c with WC and BMI was more pronounced in participants without diabetes.

These data suggest that part of the effect of obesity on LDL-c is related to a specific profile of LDL-C subfractions and that T2D and insulin resistance may play a role in the obese population, directly influencing LDL subfractions distribution. It is well known that insulin resistance and diabetes influence LDL subfraction distribution (i.e., IR promotes formation of small, dense LDL particles in the setting of lipoprotein lipase inhibition, and increased activity of hepatic lipase and cholesteryl ester transfer protein (CETP) [24, 25].Previous evidence indicates that insulin resistance is a likely bridge linking obesity to obesity-associated metabolic dyslipidemia [4]. Both insulin resistance and metabolic dyslipidemia are correlated with adiposopathy [26].

Adipokines, which are produced by adipocytes and macrophages that accumulate in adiposopathy, are considered the primary molecular mediators of obesity-related insulin resistance [27] These adipokines contribute to insulin resistance and stimulate lipolysis,

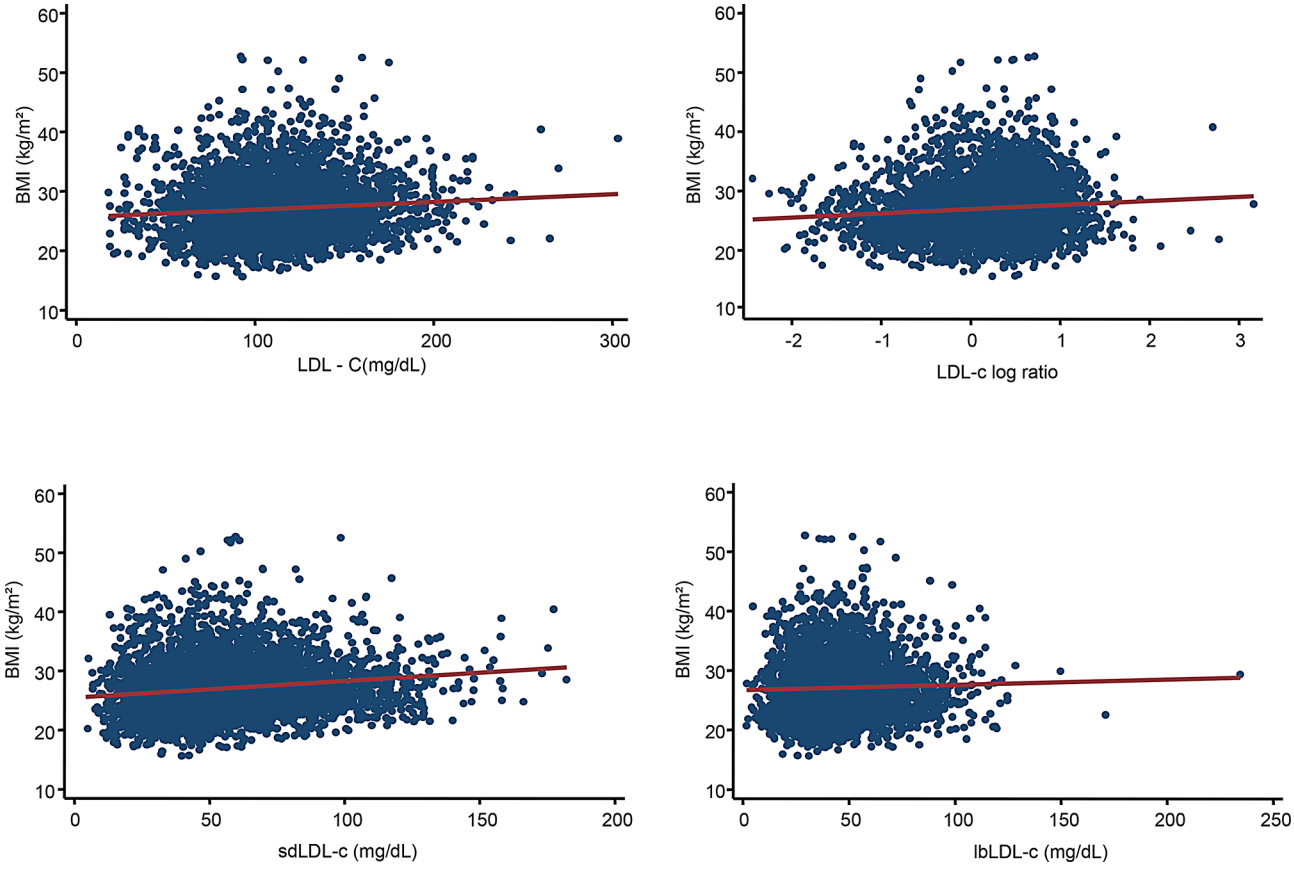

Fig. 1 Correlation between BMI and LDL-c, LDL-c log ratio, sdLDL-c, and lbLDL-c

leading to the release of free fatty acids (FFAs) into the bloodstream. The elevated concentration of FFAs can cause lipotoxicity, representing another mechanism through which obesity-related insulin resistance affects non-adipose tissues [28].

Insulin functions to suppress lipolysis in adipose tissue by inhibiting hormone-sensitive lipase (HSL), thereby regulating the release of FFAs into circulation [29]. Furthermore, insulin suppresses the secretion of very low-density lipoproteins (VLDL) from the liver [30]. In the bloodstream, insulin enhances the hydrolysis of triglycerides (TG) from VLDL particles through the action of lipoprotein lipase (LPL) and boosts hepatic lipase activity [31]. Overall, insulin promotes the degradation of TG-rich lipoproteins.

In the liver, insulin facilitates the dephosphorylation of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, which activates the enzyme and accelerates cholesterol synthesis [29]. However, in the context of insulin resistance, the plasma clearance of TG-rich lipoproteins is impaired, leading to hypertriglyceridemia. Under such conditions, the activity of cholesteryl ester transfer protein (CETP) increases the exchange of triglycerides with cholesteryl esters among lipoprotein particles. Consequently, LDL and HDL particles become enriched with triglycerides and, upon undergoing hydrolysis by plasma lipases, transform into smaller and denser particles. These structural alterations have functional implications, resulting in the accumulation of small, dense LDL (sdLDL) and dysfunctional HDL particles [32].

Dyslipidemia is the most common comorbidity associated with obesity, followed by hypertension and T2D [1]. This study performed in a multi-ethnic population confirms previous observations [5, 33, 34] of the predominance of small dense LDL pattern and its association with obesity related risk factors. The association between BMI and sdLDL-c has been addressed in the past. In some studies, only normoinsulinemic men [35] were included, in other normoinsulinemic men and normoinsulinemic women [12], in different ethnic groups and with different sdLDL analysis methodologies [36, 37]. Our data corroborate previous findings in which the higher the BMI the higher the percentage of LDL-C that is small and dense. Unlike other studies however, this used the VAP methodology and not the sdLDL particle analysis. In comparison with previous studies our data refers to a broader sample, including both gender, different ethnicities, and people with and without T2D. Finally, we also found a more intense association between sdLDL and WC than with BMI, probably because the former has

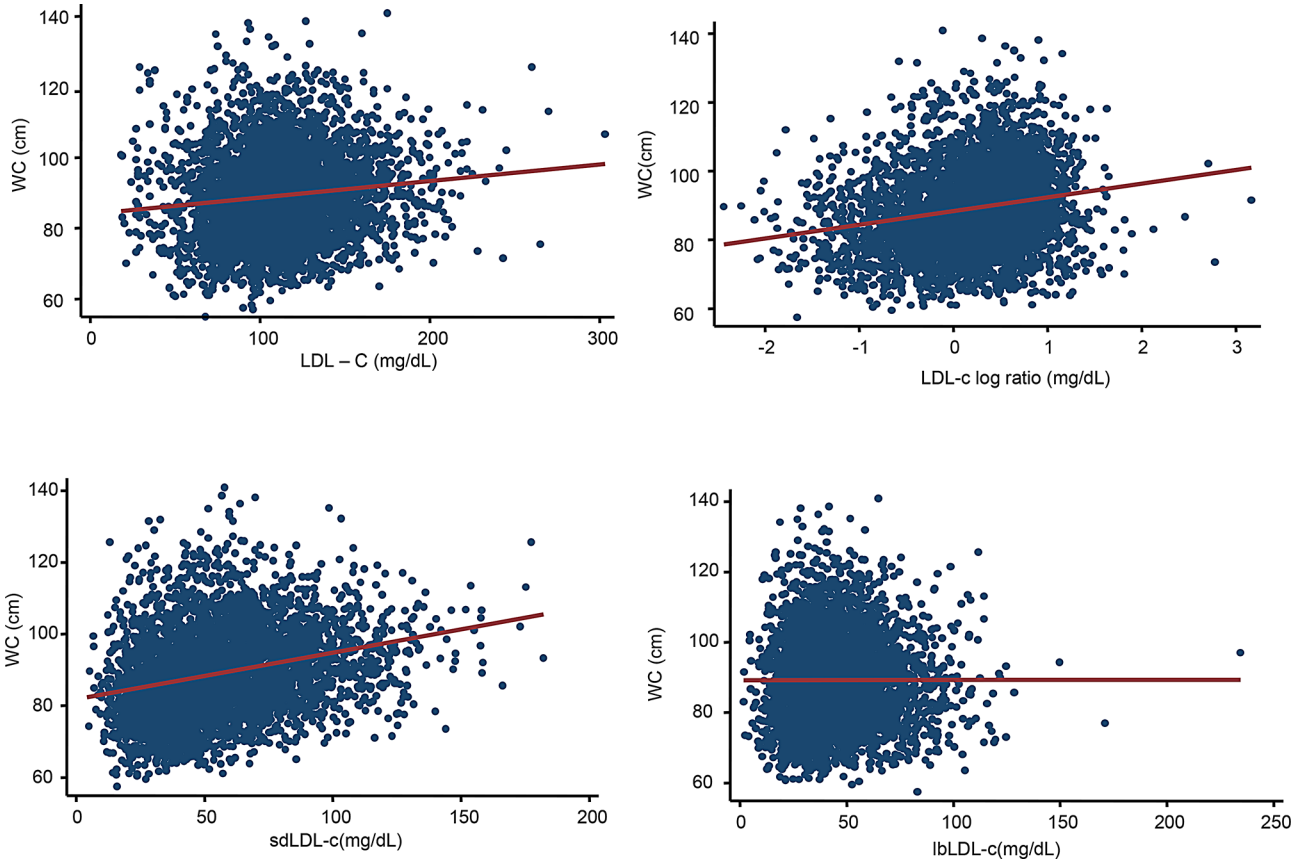

Fig. 2 - Correlation between WC and LDL-c, LDL-c log ratio, sdLDL-c, and lbLDL-c

a greater association with visceral fat while the latter with subcutaneous fat. Visceral fat is known to correlate better with metabolic abnormalities than subcutaneous fat [6, 38–42].

Previous studies show that sdLDL-c is increased in Metabolic Syndrome (MS) [43], it increases with the number of MS traits [44], and was a predictive marker of future cardiovascular and cerebrovascular events [45]. It was observed that the sdLDL-c / LDL-c ratio (reflecting total percentage of LDL that is sdLDL) correlates as well or better with MS presence than LDL-c and sdLDL-c alone.

There is a clear association between abdominal obesity and insulin resistance/hyperinsulinemia, which is the main driving force for the development of dyslipidemia in the obese [2] as well as in people with T2D and IR [46–48]. Dyslipidemia in individuals with T2D also manifests with the atherogenic pattern [14, 24, 49, 50]. The *Insulin Resistance Atherosclerosis Study* showed that WC was a strong predictor of peripheral insulin resistance in lean individuals [51]. Wang et al. [16] confirmed WC as a better predictor of T2D than BMI and the waist to hip relationship (WHR). In a large international study involving 168,000 people, Balkau et al. [10] showed that within any BMI ("normal", overweight, obese), there was a progressive increase in the prevalence of T2D in quintiles of waist circumference. Thus, the association of T2D with WC, which is a marker of visceral obesity, is evident. For this reason, the association of WC and sdLDL-c must have remained intense even after stratification for T2D in our data, while there was a loss of the strength of association with BMI, which reflects subcutaneous fat.

Relevant studies have found an association between the concentration of sdLDL particles with atherosclerosis, such as the Québec Cardiovascular Study [52] which demonstrated an association between sdLDL and ischemic coronary disease in men, and the *ARIC study*, in which sdLDL-c had association with future coronary events [53]. The combination of our findings might allow stratifying risk in the obese population with atherogenic dyslipidemia [54], with or without T2D and IR, using, in particular, waist circumference as a predictor.

Our study must be read within the context of its design. As a cross-sectional study, the described associations do not assess temporality. We enrolled only participants from the Sao Paulo center, since the VAP method was applied only to this research center. Further, as we did not use ApoB levels in this study, we cannot establish comparisons with this apoprotein, which is known to be a superior predictor of cardiovascular risk compared to

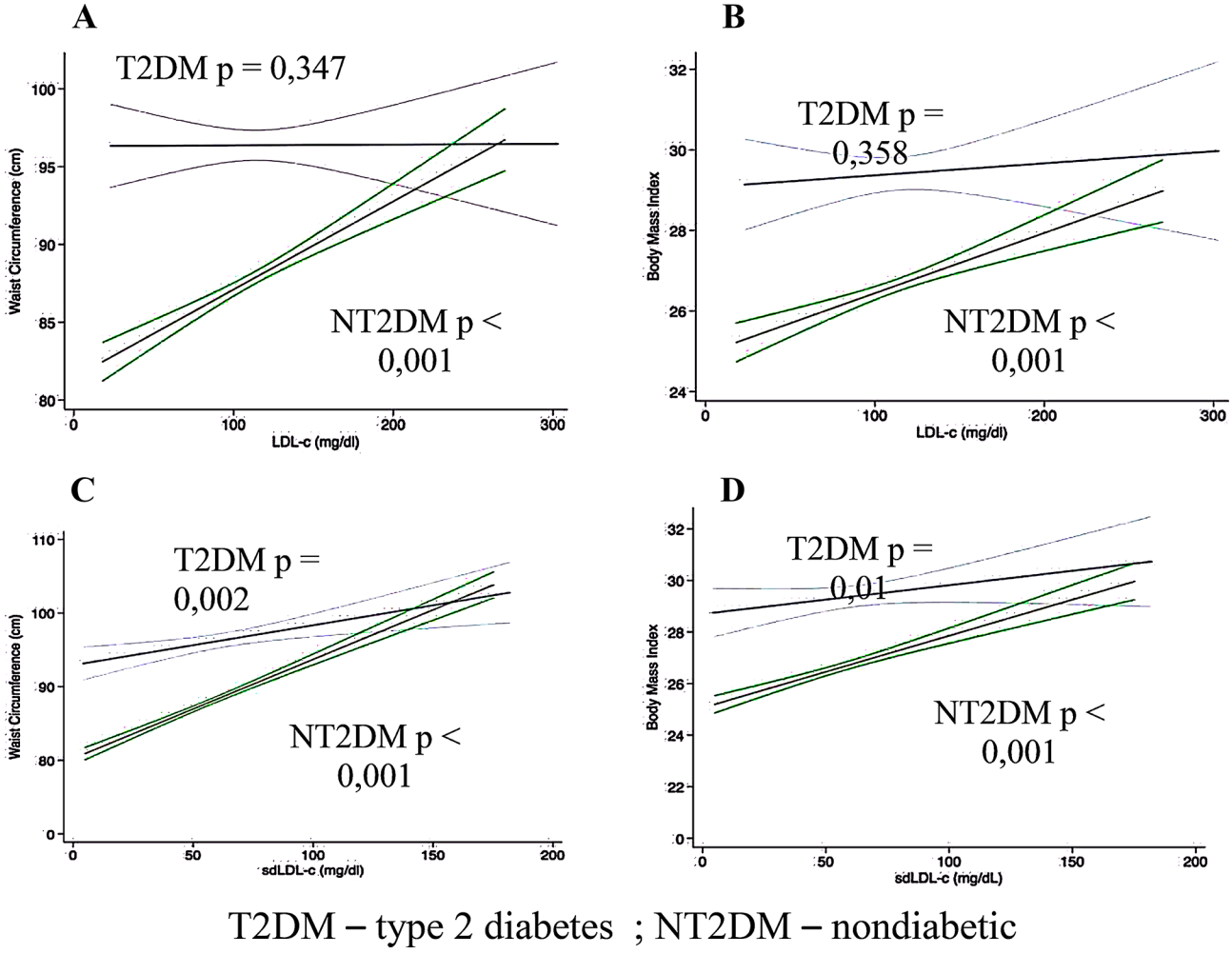

Fig. 3 Univariate association of the LDL-c and sdLDL-c with BMI and WC according to T2D diagnosis

LDL-c and non-HDL-c [55]. It should also be noted that, despite the strong correlation between ApoB, non-HDL-c, and LDL-c, there is considerable numerical variability in the latter two for a given ApoB level due to differences in their composition across various metabolic scenarios [56].

Our sample is one of our strengths since it is more heterogenous than samples of previous studies including a wider range of ages, different ethnicities, persons with T2D and smokers, for example. It is also the largest cross-sectional study to date that investigates the relationship between obesity, sdLDL-c, WC and BMI using the VAP method in a multiethnic sample of individuals with or without T2D. This study shows the importance of incorporating BMI and especially WC in clinical practice as both correlated to atherogenic hyperlipidemia in our data.

In conclusion, sdLDL-c is more associated with visceral adiposity, which was better evaluated by WC than BMI in our data. This association was even more evident in individuals without T2D.

Supplementary Information

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Supplementary Material 1

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Author contributions
EGM – wrote the manuscript; data research; reviewed and edited manuscript (corresponding author) GG – reviewed/edited the manuscript, contributed with statistics IB – reviewed / edited the manuscriptISS – reviewed / edited the manuscriptACG – reviewed / edited the manuscriptSRJ – reviewed / edited manuscriptKRK – contributed with methodsMJB – reviewed / edited manuscriptPPT – reviewed / edited manuscriptPAL – reviewed / edited manuscriptMSB – reviewed / edited manuscript; contributed with statistics Guarantors Statement: Dr. Eugenio G Moraes is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

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Not applicable.

Consent to participate
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Consent to publish
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Competing interests
The authors declare no competing interests.

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