LDL Cholesterol Rises With BMI Only in Lean Individuals: Cross-sectional U.S. and Spanish Representative Data

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OBJECTIVE

Elevated LDL cholesterol (LDLc) is not strongly associated with obesity or metabolic syndrome (MS), but this relationship repeatedly has been examined assuming a linear association. This study aimed to assess the dose-response relationship between body mass index (BMI) or waist circumference (WC) and LDLc and to evaluate its link to metabolic impairment.

RESEARCH DESIGN AND METHODS

Participants in the continuous National Health and Nutrition Examination Survey (NHANES, 1999–2010) (n = 12,383) and the Study on Nutrition and Cardiovascular Risk (ENRICA, 2008–2010) (n = 11,765), representative samples of U.S. and Spanish noninstitutionalized populations, were cross-sectionally investigated. LDLc was modeled with age- and sex-adjusted regressions, with BMI and/or WC as explanatory variables included in models as two-segment linear and natural cubic splines.

RESULTS

In NHANES and ENRICA, slopes of the BMI-LDLc association changed ($P < 0.001$) at BMI 27.1 and 26.5 kg/m^2, respectively, forming an inverted U shape. Below these BMI inflection points, LDLc rose 2.30 and 2.41 mg/dL per kg/m^2 (both $P < 0.001$). However, above said points, LDLc declined −0.37 and −0.38 mg/dL per kg/m^2 (both $P < 0.001$). The WC-LDLc relationship was similar to the BMI-LDLc relationship. Accumulation of MS traits was associated with a weakening of the positive BMI-LDLc association among lean participants (below the BMI inflection point). Aging shifted the inflection point of the BMI-LDLc relationship to lower BMI values.

CONCLUSIONS

The BMI- and WC-LDLc relationships have inverted U shapes. Diminishing associations between BMI and LDLc might indicate metabolic impairment as a result of aging or other metabolic diseases. In lean individuals, small weight losses might help to lower LDLc for cardiovascular prevention.

Overweight or obese individuals often present with metabolic syndrome (MS) (1), a criteria-based condition associated with an increased risk of diabetes and cardiovascular disease (CVD). One of the CVD risk factors linked to excess weight is atherogenic dyslipidemia, which comprises elevated triglycerides, reduced HDL cholesterol (HDLc), and smaller and denser LDLs (2) but without a clear elevation of LDL cholesterol (LDLc) (2). Atherogenic dyslipidemia is strongly associated with

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future CVD events (2–4), and this association has been attributed to the accumulation of apolipoprotein B–rich lipoproteins and impaired HDL function (5). However, the contribution of changes in triglycerides and HDLc to the development of CVD is still unclear (6), and the absence of a manifest elevation of LDLc contrasts with its essential role in atherosclerosis development. Moreover, LDLc concentration and its therapeutic modification are associated with future CVD (7) to a greater extent than triglyceride (8) or HDLc (9) concentrations. In fact, among patients with obesity or MS, LDLc reduction with statins decreases CVD events, whereas drug treatments that improve atherogenic dyslipidemia have shown no or only very modest efficacy in CVD outcomes (10).

Previous studies of the relationship between anthropometry and LDLc used relatively small or selected samples or focused on specific ethnic or age-groups (11–14). Most importantly, it is possible that the apparent lack of elevation of LDLc in individuals with excess weight results from the fact that most studies addressed the relationship as a linear association (11–15) or did not comprehensively depict the relationship, including identifying slopes and inflection points (16,17). Lower levels of all serum lipid fractions, including triglycerides, are found among morbidly obese patients (18). Nonetheless, the relationship between increasing weight and LDLc might change at early stages across the normal anthropometric range and, moreover, it might depend on metabolic status.

Thus, this study aimed, first, to assess the dose-response relationship between body mass index (BMI) or waist circumference (WC) and LDLc and, second, to describe how such a relationship varies according to the number of components of MS. To this end, we analyzed data from large nationally representative studies in the U.S. and Spain. This work may shed light onto the poorly understood relationship between anthropometry and LDLc in the general population and help to identify in which groups weight loss might improve LDLc.

RESEARCH DESIGN AND METHODS

Study Participants and Design

We analyzed cross-sectional nationally representative data from the continuous National Health and Nutrition Examination Survey (NHANES, 1999–2010) in the U.S. (19) and the Study on Nutrition and Cardiovascular Risk (ENRICA, 2008–2010) in Spain (20,21) (detailed description provided under Methods in Supplementary Data). The sample comprised NHANES participants in the fasting subsample age ≥20 years and ENRICA participants age ≥20 years, with complete data on BMI, WC, and lipids (n = 12,383 and 11,765, respectively); LDLc was not available in 307 and 127 participants in NHANES and ENRICA, respectively, and analyses that included MS criteria further excluded 352 and 186 individuals from each study. Participants in NHANES and ENRICA provided written informed consent, and both studies were approved by the appropriate ethics research committees (NHANES: National Center for Health Statistics Research Ethics Review Board, Atlanta, GA; ENRICA: Clinical Research Ethics Committees of the Hospital Universitario La Paz, Madrid, Spain, and of the Hospital Clinic, Barcelona, Spain). The NHANES data sets are available in the National Center for Health Statistics repository (www.cdc.gov/nchs/nhanes). The ENRICA data sets are not publicly available because of safeguarding individual privacy. Data are available, however, from the authors upon reasonable request and with permission of the research committee. Computing code required to replicate the results is available from the authors upon reasonable request.

Study Variables

Serum lipids and glucose from fasting blood samples and anthropometry and blood pressure were measured using standard methods (Supplementary Data, Methods). LDLc was calculated using the Friedewald equation when triglycerides were <400 mg/dL (multiply by 0.0113 to convert to mmol/L).

Statistical Analysis

The anthropometric-LDLc relationship was first explored graphically and subsequently quantified numerically. Next, joint association of BMI and WC with LDLc was explored. Finally, effect modification by metabolic status and age was studied graphically and numerically.

LDLc, as the main outcome, was modeled as a function of BMI and WC using several regression methods and various levels of adjustment for potential confounders. First, unadjusted linear and narrow-bandwidth locally weighted scatterplot smoothing (LOESS) regressions (span 0.6 [chosen so that all inflection features were shown without introducing small amplitude noise]) were used to assess graphically the study associations free of assumptions regarding shape. Second, models with natural cubic splines (with five knots [chosen to provide enough flexibility to reproduce curves similar to those in LOESS plots without introducing unnecessary noise; their location followed standard recommendations]) were fitted through age- and sex-adjusted generalized linear regressions to visualize graphically the adjusted association. Finally, we quantified the slopes across the anthropometric range and tested for differences. To that end and to identify the BMI and WC values where the inflection point in the association occurred, we fitted multiple models of age- and sex-adjusted linear splines with two straight segments. This set of models swept the anthropometric variables' ranges, testing all the possible locations for the inflection point. The models with the minimum Akaike information criterion were chosen. These linear spline models also were used to quantify the association between LDLc and BMI or WC in each segment because they encompassed enough information to describe the relationship, and their simplicity optimized the interpretation and communication of the results.

A generalized linear model that included BMI and WC as natural cubic splines and adjusted for age and sex was fitted and used to plot their simultaneous association with LDLc concentrations. In addition, linear spline models like those described above but also adjusted for BMI or WC as natural cubic splines were fitted to estimate the independent slopes at both sides of the inflection points.

To describe how the anthropometry-LDLc relationship varied according to cardiometabolic health, we performed LOESS regressions stratified by the number of MS criteria enlisted in the harmonized joint MS definition (excluding the WC criterion) (1) (Supplementary Data, Methods). In addition, by dividing the samples into nonobese and obese strata (BMI ≥30 kg/m^2) and creating age- and sex-adjusted models separately for each stratum, we studied the interaction between BMI and the number of MS criteria. This allowed us to

estimate the slope of the study association at each level of metabolic impairment (defined by the number of criteria) and to test for differences. These same analyses were repeated for age-groups (<40, 40 to <60, ≥60 years). Finally, to check the robustness of the results, we ran several sensitivity analyses. We also checked that the models' assumptions were reasonably met. All analyses, except LOESS regressions, accounted for the surveys' sampling weights and their complex sampling structure through the survey package in the R statistical software.

RESULTS

Participants in both studies had similar age and sex distributions, but those from the U.S. had higher BMI, WC, and triglycerides than those from Spain (Supplementary Table 1). LDLc had a linear weak-positive association with BMI and WC in both populations (Supplementary Table 2). In contrast, shape assumption–free LOESS regressions showed biphasic associations between BMI or WC and LDLc, with segments approximately linear at both sides of a clear inflection point (Supplementary Fig. 1). Age- and sex-adjusted models that were based on natural cubic splines confirmed this biphasic shape (Fig. 1*A* and *B*). Slopes of the association significantly changed ($P < 0.001$) at BMI 27.1 kg/m^2 in NHANES and 26.5 kg/m^2 in ENRICA; corresponding inflection values for WC were 96 and 89 cm. Among individuals below the BMI inflection point, LDLc increased 2.30 mg/dL per kg/m^2 in NHANES and 2.41 mg/dL per kg/m^2 in ENRICA (both $P < 0.001$) (multiply by 0.0259 to convert to mmol/L); corresponding increases in LDLc per 1 cm of WC were 0.83 and 0.84 mg/dL (both $P < 0.001$) (Table 1). In contrast, among those above the inflection points, LDLc decreased across BMI and WC values; LDLc was 0.37 and 0.38 mg/dL lower per kg/m^2 in NHANES and ENRICA, respectively (both $P < 0.001$); corresponding differences per 1 cm of WC were −0.26 and −0.18 mg/dL (both $P < 0.001$) (Table 1). Nonlinear models achieved a statistically significant better fit of the relationships.

When BMI and WC were mutually adjusted in a model with cubic splines, each was independently associated with an LDLc ascent among individuals below the BMI or WC inflection points (Supplementary Fig. 2*A*–*D* and Supplementary Table 3). In contrast, among those above the inflection point, no independent association was observed between BMI and LDLc (Supplementary Fig. 2*A* and *B*), but higher WC values were associated with lower LDLc (Supplementary Fig. 2*C* and *D*). Specifically, for a given BMI, a marked downward shift in the direction of the association between WC and LDLc was observed at 96.3 and 88.8 cm in NHANES and ENRICA, respectively (Supplementary Fig. 2*C* and *D* and Supplementary Table 3).

Table 2 and Fig. 2*A* and *B* show the association between BMI and LDLc according to the number of MS criteria other than high WC. For BMI values below the obesity limit (<30 kg/m^2), the ascending slope of LDLc with increasing BMI progressively flattened as the number of MS criteria increased from zero to three. For individuals with four MS criteria, LDLc seemed to be lower than for the other groups at any BMI value. Indeed, the slopes of the association of BMI with LDLc were statistically different for those with one, two, or three versus zero components of MS, particularly in ENRICA (Table 2). However, among those with BMI ≥30 kg/m^2, the association between BMI and LDLc did not vary with the number of MS criteria (Table 2).

The association between BMI and LDLc progressively flattened with increasing age for BMI <30 kg/m^2 but not above

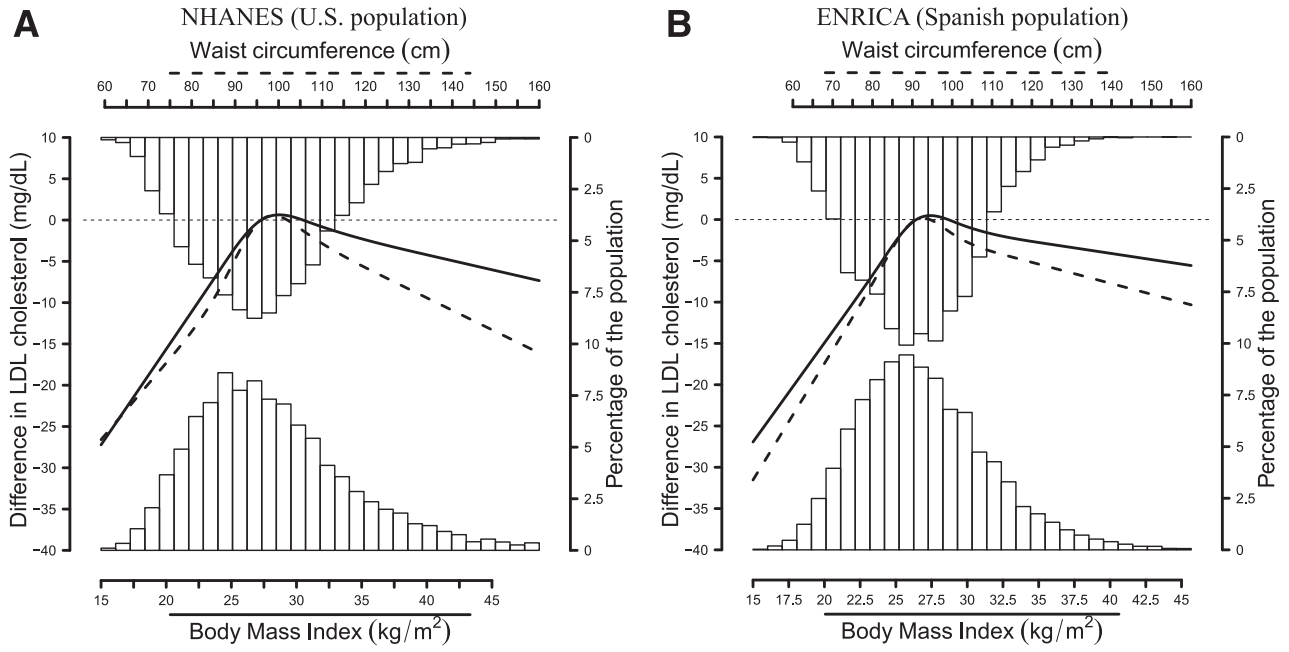

Figure 1—Natural cubic splines of LDLc according to BMI or WC, adjusted for age and sex, in the NHANES (U.S. population) (*A*) and ENRICA (Spanish population) (*B*) studies. The curves show the difference in LDLc with respect to LDLc concentration (0 reference, dotted horizontal line) at the median of BMI or WC. The solid curve shows the association of BMI with LDLc, and the dashed curve shows the association of WC with LDLc. The lower histograms show the BMI distributions in the population, and the upper inverted histograms show the WC distributions. Plots are overlapped so that first quartiles and medians of BMI and WC coincide. Curves are derived from generalized linear models using natural cubic splines adjusted for age and sex. Multiply values on the left-side *y*-axis by 0.0259 to convert to mmol/L.

Table 1—Slopes (95% CIs) of the association of BMI or WC with LDLc among individuals below or above the inflection point of the studied association: results from the NHANES (U.S. population) and ENRICA (Spanish population) studies

		LDLc slope (mg/dL per anthropometric unit)	
	Inflection point	Lower range (95% CI) (below inflection point)	Upper range (95% CI) (above inflection point)
NHANES			
BMI (kg/m^2)	27.11	2.30 (1.99, 2.61)	−0.37 (−0.54, −0.20)
WC (cm)	96.31	0.83 (0.70, 0.96)	−0.26 (−0.34, −0.18)
ENRICA			
BMI (kg/m^2)	26.46	2.41 (2.08, 2.73)	−0.38 (−0.60, −0.16)
WC (cm)	89.15	0.84 (0.73, 0.95)	−0.18 (−0.27, −0.09)

All $P < 0.001$ for slope differences between lower and upper anthropometric ranges. The data are derived from generalized linear models using linear splines, which allowed the statistical search for the optimal inflection values and adjusted for age and sex. Multiply by 0.0259 to convert to mmol/L.

(Table 2 and Fig. 2*C* and *D*). In fact, the downward inflection point seems to shift toward lower BMI values with age, from 30 kg/m^2 among participants <40 years old to 25 kg/m^2 among those ≥60 years old (Fig. 2*C* and *D*).

The main results were rather robust. Men and women as well as white and black individuals showed a tipping point for the study association at the midrange of BMI and WC values (Supplementary Data, Stratified Results by Sex and Race-Ethnicity). Similar results were obtained in analyses with non-HDLc as the dependent variable, which explored a lipid that is not inversely correlated with triglycerides and avoided excluding participants with high triglycerides in which LDLc cannot be adequately estimated (Supplementary Data, Non-HDL Cholesterol as Dependent Variable); in analyses adjusted for age, sex, race, education level, smoking, alcohol, diabetes, hypertension, and use of lipid-lowering medication (Supplementary Data, Main Tables of the Manuscript Adjusted for Extra Variables); or in analyses restricted to individuals not taking lipid-lowering drugs or following lipid-lowering diets (data not shown).

CONCLUSIONS

In this study that was performed on two population-based samples of the U.S. and Spanish populations, we found an inverted U-shaped association between BMI or WC and LDLc. The loss of association between BMI and LDLc seems to be linked with metabolic disorders as a result of aging or other metabolic diseases that promote MS. Thus, the sharp inflection point could be an early sign of metabolic impairment in the progression toward obesity after surpassing a tolerance threshold, which lowers with age.

The association between anthropometrics and LDLc was demonstrated

Table 2—Slopes (95% CIs) of the association of BMI with LDLc across participants with increasing count of MS criteria (other than WC) and across participants belonging to different age-groups in the nonobese and obese strata from the NHANES (U.S. population) and ENRICA (Spanish population) studies

	BMI <30 kg/m^2			BMI ≥30 kg/m^2		
	n	Slope (95% CI) (mg/dL per kg/m^2)	*P* value	*n*	Slope (95% CI) (mg/dL per kg/m^2)	*P* value
Count of MS criteria (other than WC)						
NHANES						
0	2,278	2.41 (1.96, 2.86)	Ref.	481	−1.00 (−1.93, −0.07)	Ref.
1	2,601	1.41 (0.87, 1.94)	0.008	983	−0.21 (−0.66, 0.24)	0.141
2	1,834	2.15 (1.42, 2.87)	0.541	1,280	−0.49 (−0.83, −0.15)	0.344
3	776	−0.73 (−1.86, 0.39)	<0.001	850	−0.60 (−1.16, −0.03)	0.448
4	296	0.54 (−1.73, 2.82)	0.107	357	0.27 (−0.71, 1.25)	0.070
ENRICA						
0	3,505	2.14 (1.74, 2.54)	Ref.	260	0.73 (−0.74, 2.19)	Ref.
1	3,195	1.78 (1.33, 2.24)	0.238	770	−0.04 (−0.79, 0.71)	0.362
2	1,498	1.22 (0.48, 1.96)	0.031	815	−0.37 (−1.04, 0.30)	0.186
3	578	0.03 (−1.55, 1.62)	0.012	509	−0.34 (−1.27, 0.60)	0.232
4	138	−0.27 (−2.97, 2.43)	0.085	184	0.06 (−1.20, 1.33)	0.504
Age-group						
NHANES						
<40 years	2,929	2.39 (1.94, 2.83)	<0.001	1,324	−0.62 (−0.99, −0.24)	0.923
40 to <60 years	2,383	1.61 (1.11, 2.12)	0.006	1,391	−0.40 (−0.78, −0.01)	0.612
≥60 years	2,672	0.49 (−0.06, 1.04)	Ref.	1,377	−0.58 (−1.19, 0.03)	Ref.
ENRICA						
<40 years	3,348	2.14 (1.76, 2.52)	<0.001	465	−0.21 (−1.08, 0.65)	0.781
40 to <60 years	3,530	1.76 (1.29, 2.23)	<0.001	1,061	−0.46 (−1.04, 0.13)	0.360
≥60 years	2,177	−0.29 (−0.82, 0.25)	Ref.	1,057	−0.07 (−0.67, 0.54)	Ref.

The slopes are derived from generalized linear models of the interaction between BMI and the number of MS criteria and interaction between BMI and age-group. Models were correspondingly adjusted for age and sex or only for sex, and they were created separately for each obesity stratum. Differences between the slopes of the groups with the reference (Ref., zero criteria or elder group, respectively) were tested by observing the interaction term *P* value. Multiply by 0.0259 to convert to mmol/L.

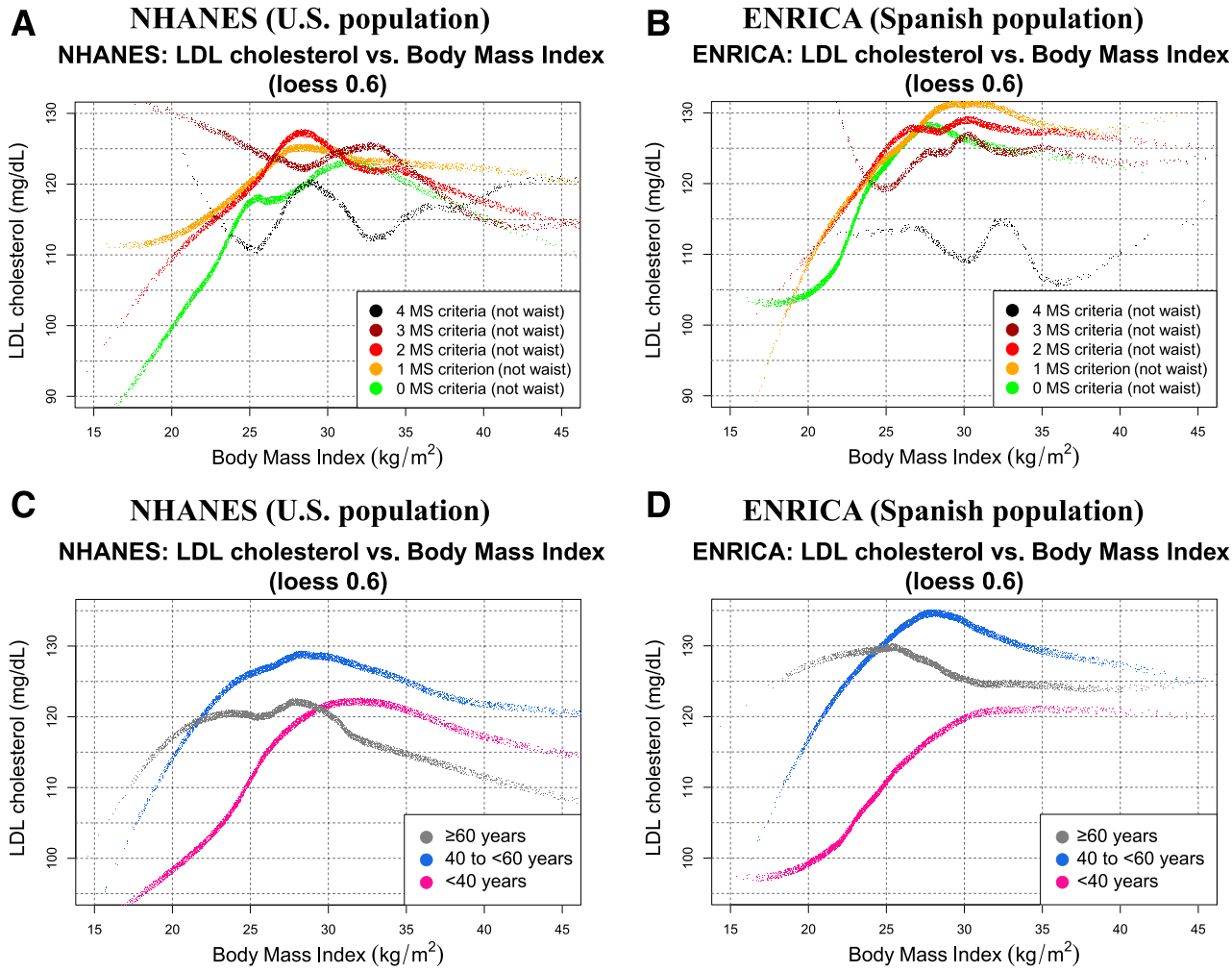

Figure 2—LOESS regressions of LDLc on BMI by strata that were based on the number of MS criteria (other than the WC criterion) (*A* and *B*) and by age strata (*C* and *D*) in the NHANES (U.S. population) and ENRICA (Spanish population) studies. For each survey participant, the dots show a prediction of their LDLc concentration on the basis of LOESS models. Multiply values on the left-side *y*-axis by 0.0259 to convert to mmol/L.

only occasionally in previous studies (22). This association has been traditionally described as weak (2) or as mostly focusing on the composition change of LDL particles with its associated differences in density (2). Of note, studies in societies less prone to obesity (12) and in children (13) have reported a positive association between anthropometrics and LDLc more often than investigations in adults from western countries. In line with previous literature (14,16,17), in the current study, the strongest direct association between higher anthropometrics and higher LDLc in leaner individuals was found in the youngest patients. The absence of linearity in the association between weight and total and non-HDLc had been previously reported in a large meta-analysis of 57 prospective studies (23), and among morbidly obese patients, all lipids, including triglycerides, seem to decrease (18). An inverted U-shape relationship between BMI and LDLc and apolipoprotein B also was shown among Native Americans without diabetes in the Strong Heart Study (22). Although the pattern also can be recognized retrospectively in the data reported from NHANES II (16,17), we make four substantial contributions to the literature: an estimate of the inflection points that relies on nationally representative data, a detailed quantification of ascending and descending slopes through dose-response analyses, a characterization of the relevance of the ascending BMI-LDLc association with respect to MS, and a contextualization of this biological phenomenon within the current obesity epidemic.

LDLc is a well-established determinant of CVD (7), and obesity is associated with excess CVD risk. However, in a large pooled analysis of the major contributors to the association between obesity and CVD, total cholesterol ranked last, far behind blood pressure and glucose, which explained ~40% of the excess risk of coronary heart disease per BMI unit, whereas cholesterol explained only an additional 5% (15). The authors analyzed all the variables in that study linearly. BMI and WC have a similar association with CVD (24), and understanding the changes in LDLc with increasing BMI or WC might help us to anticipate the reduction in LDLc that might be achieved through weight loss in clinical practice. Clinical trials could focus on ranges where a more intense effect can be expected. The current data suggest that mildly overweight or even normal weight individuals at high CVD risk might benefit from interventions that lead to weight loss resulting in LDLc reductions if the cross-sectional association that we found is confirmed in longitudinal studies.

On the contrary, among obese patients, the limited weight loss (5–10%) usually achieved in clinical practice (25) would not provide a similar benefit, underscoring the importance of prevention of weight gain from the very beginning. This could precede or add to existing lipid-lowering strategies, which include lifestyle modification, statins, fibrates, niacin, ezetimibe, cholesteryl ester transfer protein inhibitors, and proprotein convertase subtilisin-kexin type 9 inhibitors.

A number of alterations of the lipid metabolism associated with obesity and MS may explain the sharp truncation of the BMI-LDLc association. Because this phenomenon was previously overlooked, we can only speculate on some mechanisms that might explain it, but these hypotheses may set a path for future research to confirm them. A simplistic explanation pointing to raising triglycerides with weight gain does not hold because we found very similar results when analyzing non-HDLc, which does not negatively correlate with triglycerides. Atherogenic dyslipidemia is mainly the result of an increased synthesis of VLDL particles by the liver and the subsequent abnormal management of this VLDL overload (26). VLDL particles contain both triglycerides and cholesterol; among individuals with obesity and insulin resistance, triglyceride-rich and cholesterol-poor VLDL1 particles predominate in contrast to healthy individuals, who have mostly triglyceride-poor VLDL2 particles (27). Normal adipogenesis in lean individuals implies rapidly unloading fatty acids from triglyceride-rich particles by the lipoprotein lipase, which converts them into cholesterol-rich IDL and LDL. Thus, weight gain is associated with increments in these lipid fractions. However, when efficiency of lipid deposition in the adipose tissue is reduced as a result of reaching functional limits or other endocrine conditions (e.g., insulin-deficient diabetes), triglycerides may stagnate in VLDL, with a consistent decrease in LDL particle formation as we previously hypothesized (28). The current results suggest that the mentioned twist in VLDL types occurs rather abruptly in terms of anthropometric increase among individuals who are just mildly overweight. In addition, this explanation is consistent with the observed impairment of the BMI-LDLc association across the progressive increase in the number of MS traits. When MS traits are present among lean individuals, the BMI-LDLc slope is reduced, suggesting that the inflection point might have occurred at lower BMI values perhaps because of individual susceptibility, such as in lipodystrophy where the adipose tissue is reduced or in polycystic ovary syndrome where an adverse hormonal environment impairs lipid clearance. Stratified LOESS plots support this hypothesis because the inflection appears progressively in lower BMI values with increasing metabolic impairment as well as with aging. In the extreme group with four MS traits, LDLc is reduced across the BMI range, just as if the inflection occurred at a very low BMI value, out of sight in the plot. These findings are consistent with the hypothesis that MS ensues from surpassing the adipose tissue functional capacity (28). In addition, genetic variants that limit cholesterol absorption or endogenous synthesis (29), and cholesterol synthesis suppression through drugs (30), both increase the prospective risk of diabetes. It seems that the amount of cholesterol available for lipid transport, which ultimately will result in higher LDLc, may be important to preserve metabolic health and avoid diabetes.

Another possible hypothetical explanation for the inverted U-shape association between BMI or WC and LDLc (particularly for its descendent upper-range segment) derives from the fact that adipose tissue contains large amounts of cholesterol. In obese adults, >50% of total body cholesterol is located in adipocytes (31), even though the capacity of cholesterol synthesis of adipocytes is extremely low. Cholesterol deposits in adipose tissue might buffer cholesterol overload from the liver. Actually, in obesity, the activity of the LDL receptor in adipose tissue increases, and cholesterol efflux to HDL decreases. Adipose tissue already has been suggested to be a triglyceride-buffering organ (32), but normal LDLc concentration in the presence of cholesterol overproduction in obesity could indicate a role of increased fat mass in cholesterol homeostasis. Another observation that is consistent with this hypothesis is the progressive increase in biliary cholesterol secretion described during fat accumulation in obesity (33). The current study does not provide insight to support or refute this hypothesis, and new laboratory and experimental data will be needed to further clarify the origin of our results. If future research proves that this hypothesis is the reason for our findings, it should be taken into account in explaining the obesity paradox.

The main strength of this study is that it relied on high-quality data from nationally representative samples in two large countries. These data allowed us to reproduce the results in two independent populations with potential cross-cultural metabolic differences. The main study limitation was the use of cross-sectional data; thus, neither causation nor directionality of the associations can be directly assumed from the results. Consequently, these associations should be confirmed in longitudinal studies. In addition, we used calculated LDLc because it was not measured by a direct method in the health surveys, and we did not have measurements of LDL particle size, which could have provided more insight into our findings. The use of MS criteria count as an instrument to measure the degree of metabolic impairment was limited by the unspecific nature of each criterion alone but provided enough information to describe slope differences in the BMI-LDLc relationship. Future studies could rely on more-precise laboratory measurements to estimate better specific aspects of metabolic impairment.

In conclusion, LDLc rises with BMI in the range of <27 kg/m^2, and above this value, LDLc levels off or even decreases with increasing BMI. A similar dose-response relationship occurs for WC. These results are consistently found in the U.S. and Spanish populations, in both sexes, and in white and black individuals. A progressive impairment of this LDLc rise with BMI in lean individuals associates with the increasing presence of MS traits, suggesting that it could be an early sign of metabolic disorder. The BMI-LDLc association among lean individuals attenuates or even disappears with age, suggesting that it may be a marker of metabolic youth. Finally, the inverted U shape of the BMI-LDLc relationship suggests that normal weight or mildly overweight individuals would potentially reduce their LDLc by the relatively small weight losses that are realistically achieved in clinical practice. Further research should confirm

through longitudinal studies these associations and evaluate the usefulness of controlled weight loss as a potential lipid-lowering strategy among normal-weight patients with hypercholesterolemia, assess the value of BMI-LDLc metabolic inflexibility as a marker of metabolic impairment, and study the pathogenic mechanisms that produce it with aging and weight gain.

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