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Original Research Article

Increased low-density lipoprotein cholesterol on a low-carbohydrate diet in adults with normal but not high body weight: A meta-analysis

Adrian Soto-Mota [1,2,†], Yuscely Flores-Jurado [1,3,†], Nicholas G Norwitz [4], David Feldman [5], Mark A Pereira [6], Goodarz Danaei [7], David S Ludwig [4,7,8,*]

[1] *Metabolic Diseases Research Unit, National Institute for Medical Sciences and Nutrition Salvador Zubiran, Mexico City, Mexico;* [2] *Tecnologico de Monterrey, School of Medicine, Mexico City, Mexico;* [3] *National Autonomous University of Mexico, School of Medicine, Mexico City, Mexico;* [4] *Harvard Medical School, Boston, MA, United States;* [5] *Citizen Science Foundation, Las Vegas, NV, United States;* [6] *Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, MN, United States;* [7] *Harvard T.H. Chan School of Public Health, Boston, MA, United States;* [8] *New Balance Foundation Obesity Prevention Center, Boston Children's Hospital, MA, United States*

A B S T R A C T

Background: Low-density lipoprotein (LDL) cholesterol change with consumption of a low-carbohydrate diet (LCD) is highly variable. Identifying the source of this heterogeneity could guide clinical decision-making.

Objectives: To evaluate LDL cholesterol change in randomized controlled trials involving LCDs, with a focus on body mass index (BMI) in kg/m^2.

Methods: Three electronic indexes (Pubmed, EBSCO, and Scielo) were searched for studies between 1 January, 2003 and 20 December, 2022. Two independent reviewers identified randomized controlled trials involving adults consuming <130 g/d carbohydrate and reporting BMI and LDL cholesterol change or equivalent data. Two investigators extracted relevant data, which were validated by other investigators. Data were analyzed using a random-effects model and contrasted with results of pooled individual participant data.

Results: Forty-one trials with 1379 participants and a mean intervention duration of 19.4 wk were included. In a meta-regression accounting for 51.4% of the observed variability on LCDs, mean baseline BMI had a strong inverse association with LDL cholesterol change [β = –2.5 mg/dL/BMI unit, 95% confidence interval (CI): –3.7, –1.4], whereas saturated fat amount was not significantly associated with LDL cholesterol change. For trials with mean baseline BMI <25, LDL cholesterol increased by 41 mg/dL (95% CI: 19.6, 63.3) on the LCD. By contrast, for trials with a mean of BMI 25–<35, LDL cholesterol did not change, and for trials with a mean BMI ≥35, LDL cholesterol decreased by 7 mg/dL (95% CI: –12.1, –1.3). Using individual participant data, the relationship between BMI and LDL cholesterol change was not observed on higher-carbohydrate diets.

Conclusions: A substantial increase in LDL cholesterol is likely for individuals with low but not high BMI with consumption of an LCD, findings that may help guide individualized nutritional management of cardiovascular disease risk. As carbohydrate restriction tends to improve other lipid and nonlipid risk factors, the clinical significance of isolated LDL cholesterol elevation in this context warrants investigation.

This trial was registered at PROSPERO as CRD42022299278.

Keywords: atherosclerosis, body mass index, LDL cholesterol, saturated fat, lipid energy model, low-carbohydrate diet

Introduction

Interest in low-carbohydrate diets (LCDs) has grown among not only people with high BMI for treatment of obesity and type 2 diabetes [1] but also the general public for conditions not directly related to obesity, such as inflammatory bowel disease, mental health disorders, and neurological disease [2]. However, adoption of an LCD has been limited in part because of concern for elevation of LDL cholesterol [3], a cardiovascular disease risk factor.

Some but not all clinical trials show marked LDL cholesterol elevation soon after initiation of an LCD, and the source of this heterogeneity is poorly understood. Beyond conventionally recognized dietary factors (especially saturated fat and soluble fiber), net carbohydrate intake may also affect LDL cholesterol by impacting

Abbreviations: IPD, individual patient data; LCD, low-carbohydrate diet; LMHR, lean mass hyper-responder; RCT, randomized controlled trial.

* Corresponding author.

E-mail address: david.ludwig@childrens.harvard.edu (D.S. Ludwig).

† AS-M and YF-J contributed equally to this work.

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lipoprotein trafficking. With carbohydrate restriction, increased reliance on systemic triglyceride trafficking to meet energy demands and replenish adipocytes may cause an increase in hepatic VLDL production and subsequent increased peripheral turnover by lipoprotein lipase at adipocytes and oxidative tissues, with a resulting increase in apolipoprotein B lineage lipoproteins. This phenomenon may be most evident in individuals with lower adiposity, giving rise to the phenotypic hypothesis of "lean mass hyper-responders" (LMHR) [4].

In a cohort of 548 people restricting carbohydrate intake, BMI was inversely associated with LDL cholesterol [3], but this study is limited by the self-reported nature of dietary assessment and potential selection bias. The current study aimed to determine whether individuals with lower BMI experience a greater increase in LDL cholesterol after carbohydrate restriction. This information could help guide personalized nutritional therapy of diet-related disease, consistent with NIH priorities [5], and also inform understanding of the mechanisms relating diet to lipoprotein metabolism.

Methods

Overview and design considerations

We conducted a systematic review for clinical trials, including an LCD arm, published between 1 January, 2003, and 20 December, 2022, following preregistration on 19 January, 2022 (PROSPERO, CRD42022299278). The primary analyses examined the relationship between mean baseline BMI and LDL cholesterol change on the LCD. In additional analyses with individual participant data (IPD), we compared LDL cholesterol change on an LCD and higher-carbohydrate diet.

Our analyses focused on change within the LCD arm of the trials (pre-post), an approach that avoids the heterogeneity that would arise from comparisons of change between trial arms in view of the variety of comparison conditions employed in our sample (Supplemental Table 1). This design may also facilitate clinical translation, as the data reflect the changes from the habitual diets among participants rather than compared with comparison arms that might differ from prevailing dietary and nondietary conditions. A disadvantage of this design is potential confounding from time-varying covariates. However, we can control for ostensibly the most important such covariate, weight change, and we have no reason to believe other time-varying covariates act differently among clinical trials as a function of baseline BMI. Of note, the results of both potential designs (pre-post and between-group comparisons) remain susceptible to other sources of confounding because participants cannot be randomly assigned to different baseline BMI levels, as further considered in the Discussion.

Search strategy

Because the definition of an LCD varies among trials, we used a physiologically based criterion of <130 g carbohydrate/d [6]. Thus, PICO parameters were defined as follows:

- Participants: Adults ≥18 y, BMI 18.5–24.9.
- Intervention: LCD, with net carbohydrate (i.e., excluding dietary fiber) intake <130 g/d.
- Comparators: Adults with overweight (BMI 25–29.9), class I obesity (BMI 30–34.9), and class II or III obesity (≥35).
- Outcome: Change in blood concentration of LDL cholesterol comparing before and after LCD.

Electronic database searches for candidate studies were conducted on Pubmed, EBSCO, and Scielo, including publications in English and Spanish. Disagreements about whether to include a trial were resolved by reviewing Original Articles and Discussion among the reviewers. The reference lists of the selected trials and other systematic reviews [7–12] were reviewed to complement the search for eligible studies. Because saturated fat consumption is presently considered a major contributor to LDL cholesterol elevation, and because 2 cross-over trials had 2 eligible arms, we excluded the arms with the lower saturated fat intakes to avoid inclusion of some participants more than once.

Values for LDL cholesterol reported in mmol/L were converted to mg/dL by multiplying by 38.67. Energy intake values reported in kilojoules were converted to kilocalories by multiplying by 0.24. Intake of carbohydrates and saturated fat in grams were calculated from percentage of energy intake. Sixteen trials reported LDL cholesterol change SE or equivalent information. For the other trials, SEs for LDL cholesterol change were imputed using baseline and final LDL cholesterol variance, adjusting for their correlation in each BMI category.

Selection criteria and data extraction

Inclusion.

- Randomized control trials (RCTs).
- Restriction of net carbohydrate consumption to <130 g/d in ≥1 study arm. If this degree of carbohydrate restriction was achieved only up to an intermediate time point, the trial was included, and the intermediate value was used.
- Carbohydrate intake during intervention (in grams or as a proportion of total energy) was reported (i.e., adherence).
- Mean baseline BMI (or height and weight) was reported.
- Intervention duration ≥2 wk.

Exclusion.

- Interventions with multiple components (e.g., exercise) that could confound outcomes.
- Trial included pregnant or lactating females or children <18 y.

Two investigators independently extracted data from each study into an Excel spreadsheet and met to resolve discrepancies. The database was reviewed by 3 other investigators for accuracy.

Descriptive statistics

Data cleaning and statistical analyses were performed using R version 4.0.3 and the packages: *metafor, ggstatsplot, performance, and dplyr.*

Meta-analyses methods

A meta-regression (adjusted for saturated fat intake, carbohydrate intake, and weight change) to assess the effect of BMI on LDL cholesterol change was built using the function *metafor::rma(mods=~)*. We performed random-effects meta-analyses for BMI categories using *metafor::rma(method="REML")* [13] as our main approach to examine the relationship between BMI category and LDL cholesterol change. Meta-analyses were also performed with the DerSimonian-Laird method.

Publication bias was evaluated with Egger's test [14] (which measures the relationship between effect size and its standard error) using m*etafor::regtest(model=" lm")*. The Failsafe-N (the number of trials averaging a Z-value of 0 that would be needed to add to the meta-analysis to revert the statistical significance of the pooled-effect size) was calculated using Rosenthal's test with the function *metafor::fsn(type="Rosenthal")* [15].

Sensitivity analyses were performed with the function *metafor::leave1out,* which yields the output of every meta-analysis after removing 1 trial iteratively. Additionally, to evaluate if the observed negative association between BMI and LDL cholesterol change was because of statins, analyses were repeated after excluding trials in which participants used statins.

Pooled individual-level data analyses

Because inferences about the relationship between variables at the individual level with the results from meta-analysis may be susceptible to ecological fallacy [16], we obtained anonymized IPD from the public repository of the Diet Intervention Examining The Factors Interacting with Treatment Success (DIETFITS) Study at Open Science Framework (https://osf.io/ztysq), in which BMI ranged from 28 to 40. To obtain a broader BMI range, we contacted corresponding authors of trials with mean BMI <25, 2 of whom responded [17,18].

We compared the IPD regressions with the meta-regression lines using *ggplot2::geom_smooth*, which produces local polynomial regression fitting with fewer than 1000 observations. We used the control groups from the trials with available IPD [17–19] to determine whether the negative association between BMI and LDL cholesterol change was specific to LCDs.

We also measured and compared the influence of BMI and saturated fat intake across different carbohydrate intake levels. Because BMI units and gram changes in saturated fat intake are not directly comparable, we categorized BMI by 4 WHO categories [20] and saturated fat intake by quartiles. We used an orthogonal polynomial regression model, having previously hypothesized [4] and observed [3] a nonlinear association between BMI and LDL cholesterol. The differences in effect size were tested using the function *ggstatsplot::ggcoefstats,* which produces a forest plot with the effect size of every variable level using the first saturated fat intake quartile and class I obesity as null effect reference categories.

Postregistration protocol changes

Three post hoc changes were made as follows. *1*) We originally planned to include in the study sample not only RCTs but also observational studies (cohort, case-control, and cross-sectional). However, our initial literature search focused on RCTs yielded substantially more individual studies than expected (Figure 1), and these had participants representing a wide range of mean baseline BMI categories. Therefore, we decided to exclude other studies with an observational design, as these would be more susceptible to selection bias. Thus, our final sample of RCTs involved participants who had not self-selected an LCD and had agreed to accept randomly assigned assignments among ≥2 different treatments. *2*) With the unexpected power to do so, we conducted separate meta-analyses for class I obesity and class II-III obesity. *3*) We obtained IPD to confirm and extend findings from the meta-analysis.

Patient and public involvement

The study was conducted without involvement of patients or the public. However, all data and analysis code will be freely available to patients and the public, as below.

Results

Forty-one trials were eligible, including 4 with 2 eligible arms, yielding a total of 45 LCD arms. These trials had 1379 participants and a mean intervention duration of 19.4 wk (range 4–104 wk). The PRISMA 2009 [21] workflow for study screening and selection is depicted in Figure 1. Supplemental Table 1 summarizes the main characteristics and variables of interest among the eligible studies.

A meta-regression (Table 1) including BMI, net carbohydrate intake, saturated fat intake, and weight change explained 51.4% of the variability in LDL cholesterol change on the LCDs. Among these variables, BMI was strongly associated with LDL cholesterol change [95% confidence interval (CI): –3.7, –1.4], whereas saturated fat was weakly associated (95% CI = 0.0–0.4).

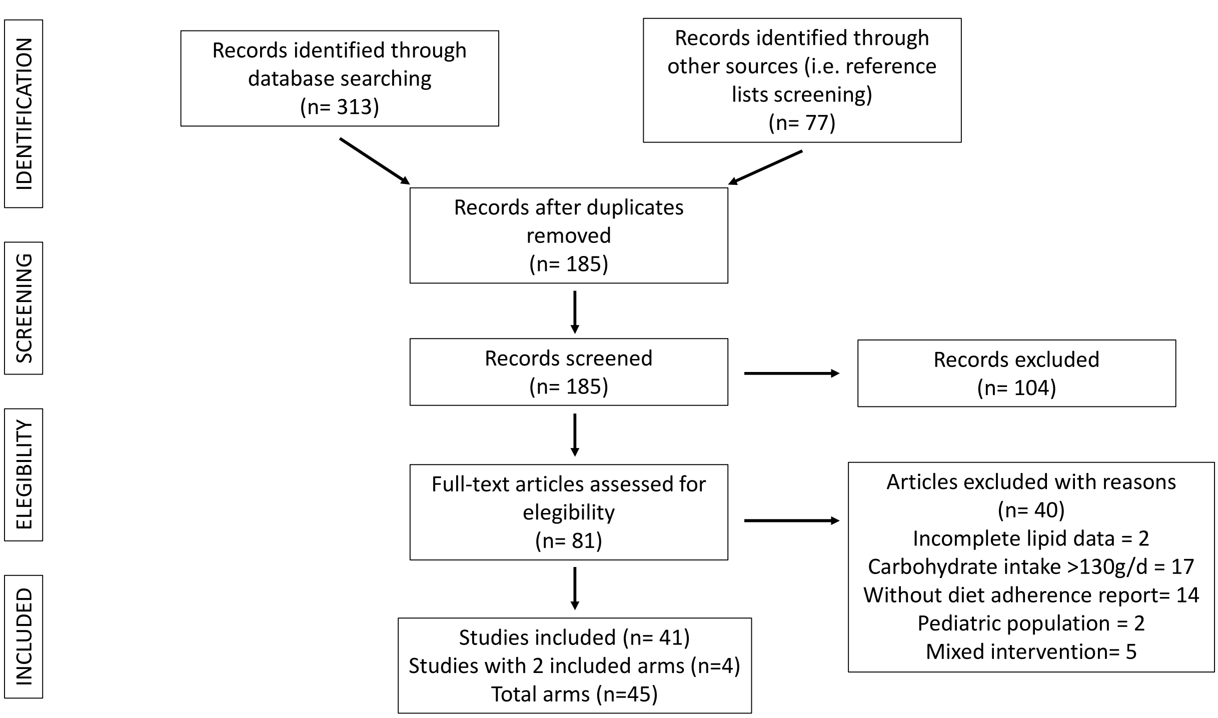

FIGURE 1. Study flow chart. PRISMA study selection workflow. PRISMA, preferred reporting items for systematic reviews and meta-analyses.

TABLE 1
Meta-regression analysis of LDL cholesterol change (mg/dL) including 45 low-carbohydrate diet trial arms, n = 1379 participants

	Estimate	SE	Z-value	95% CI
Intercept	72.5	18.8	3.9	35.7–109.4
BMI (kg/m^2)	–2.5	0.6	–4.3	–3.7 to –1.4
Carbohydrate intake (g/d)	–0.1	0.1	–0.8	–0.2 to 0.1
Saturated Fat intake (g/d)	0.2	0.1	1.9	0.0–0.4
Weight change (kg)	1.4	0.7	2.0	0.0–2.8
			I^2 = 96.9%	R^2 = 51.4%

Abbreviations: BMI, body mass index; CL, confidence interval; LDL, low-density lipoprotein; SE, standard error.

Forest plots of the meta-analyses showed marked differences among BMI categories (Figure 2). LDL cholesterol increased substantially in trials with mean baseline BMI in the healthy range (41.4 mg/dL; 95% CI: 19.6, 63.3). In contrast, LDL cholesterol decreased moderately in trials with a mean BMI of at least class II obesity (–6.7 mg/dL; 95% CI: –12.1, –1.3). For trials with BMI in the intermediate ranges (overweight or class I obesity), LDL cholesterol did not change. Similar results were obtained with the DerSimonian-Laird method (see publicly available code).

Publication bias visual and statistical tests were negative (Supplemental Figure 1), and sensitivity analyses showed the pooled-effect results would not change with the exclusion of any individual study from the meta-analysis of any BMI class. For meta-analyses with statistically significant effect sizes, the fail-safe-N tests suggest the findings were robust to publication bias (Supplemental Tables 2–5). Removing the 3 trials [22–24] that enrolled participants using statins did not materially change the meta-regression results (Supplemental Table 6).

We obtained IPD from 328 participants, representing 23% of the total participants in the eligible studies. Figure 3 shows regression plots for both meta-regressions (with and without trials using statins) and both IPD analyses (with and without carbohydrate restriction). The inverse relationship between BMI and LDL cholesterol change was present in the analyses of an LCD (panels A–C) but not in the analysis of a higher-carbohydrate diet (panel D). To explore this effect, we made a prediction-based comparison of the influence of BMI and saturated fat intake using IPD (Figure 4). Among participants consuming an LCD, BMI had a substantially larger influence than saturated fat on LDL cholesterol change. In Supplemental Figure 2, comparing each BMI category and saturated fat intake quartile, the exceptional influence of BMI on an LCD is evident. The effect size of healthy BMI on LDL cholesterol change was larger than the effect size of the top saturated fat intake quartile (48 compared with 9 mg/dL). Among participants consuming a higher-carbohydrate diet, the influence of BMI was much reduced and similar to saturated fat (4 compared with 4 mg/dL). These results did not change with adjustment for weight change during the trials (Supplemental Figure 2C and D).

Discussion

These results demonstrate an inverse association between BMI and LDL cholesterol change with consumption of an LCD. Whereas lean individuals experience marked elevation of LDL cholesterol, those with high BMI typically experience no change or a reduction in LDL cholesterol. Furthermore, the importance of BMI in explaining response heterogeneity appeared much greater than saturated fat. Our findings are consistent with recent data from others [3,25,26] and contradict

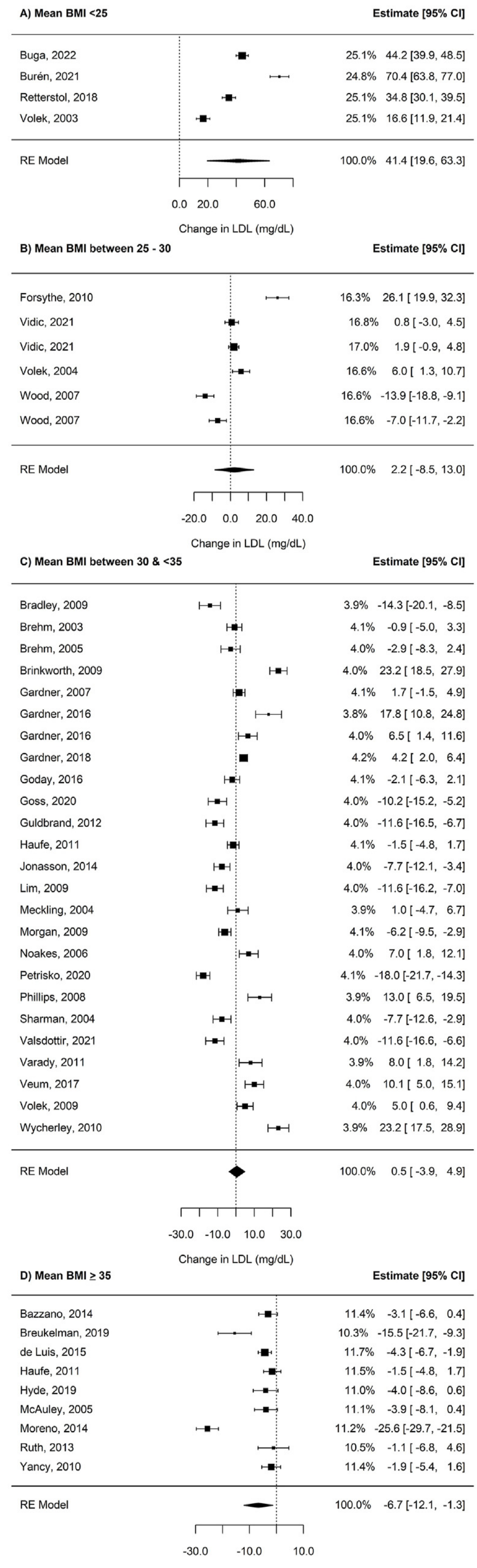

FIGURE 2. Meta-analyses of LDL cholesterol change by mean baseline BMI category. (A) Healthy BMI (kg/m^2). (B) Overweight. (C) Obesity class I. (D) Obesity class II and III. All analyses used the DerSimonian-Laird method. BMI, body mass index; CI, confidence interval; LDL, low-density lipoprotein; RE, random effects.

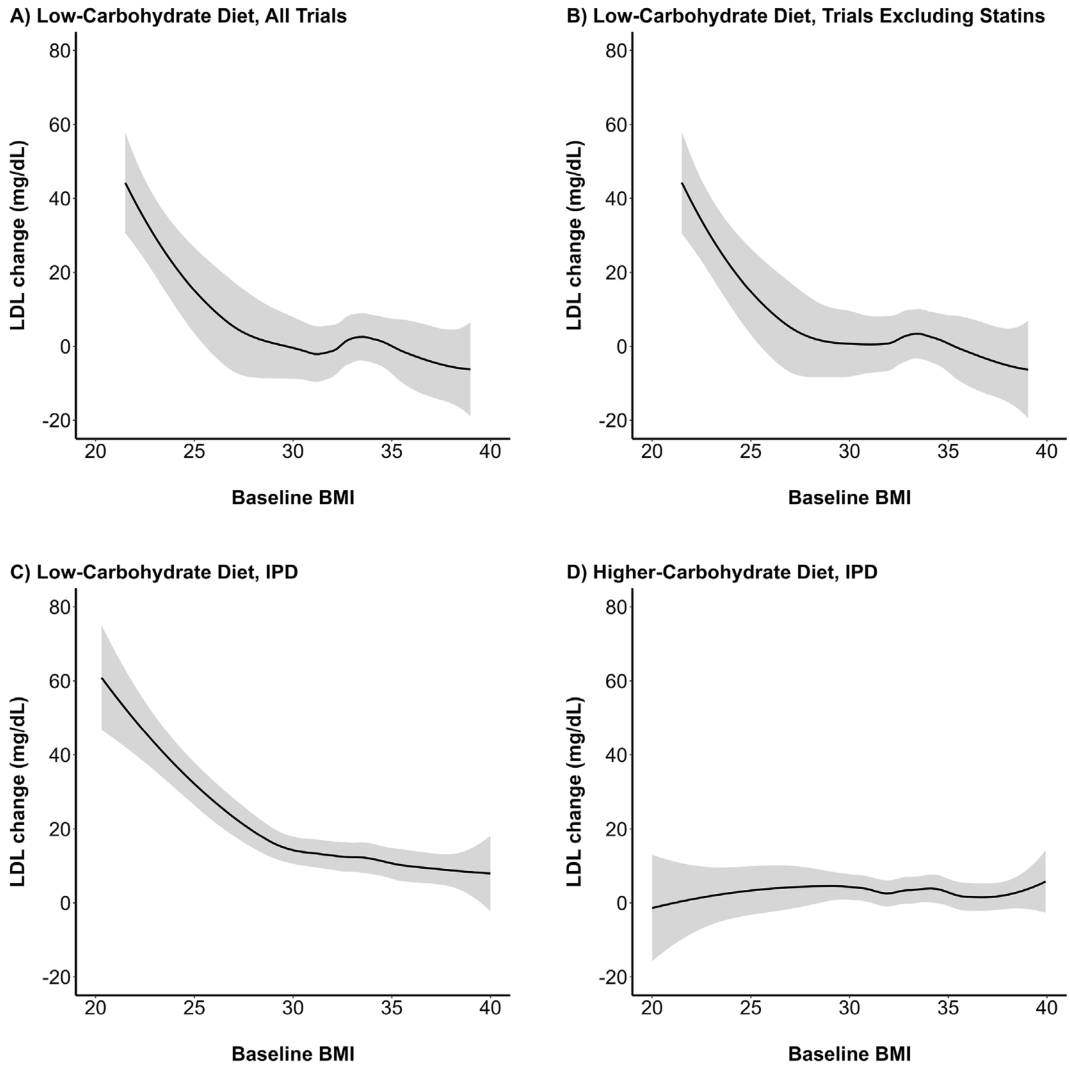

FIGURE 3. Relationship between mean baseline BMI and LDL cholesterol change. (A) Low-carbohydrate diet, including all eligible trials. (B) Low-carbohydrate diet, excluding trials in which participants were statin-treated. (C) Low-carbohydrate diet, individual participant data (IPD), $n = 328$. (D) Higher-carbohydrate, IPD, $n = 312$. Regression line produced using ggplot2::geom_smooth(A). BMI, body mass index; LDL, low-density lipoprotein.

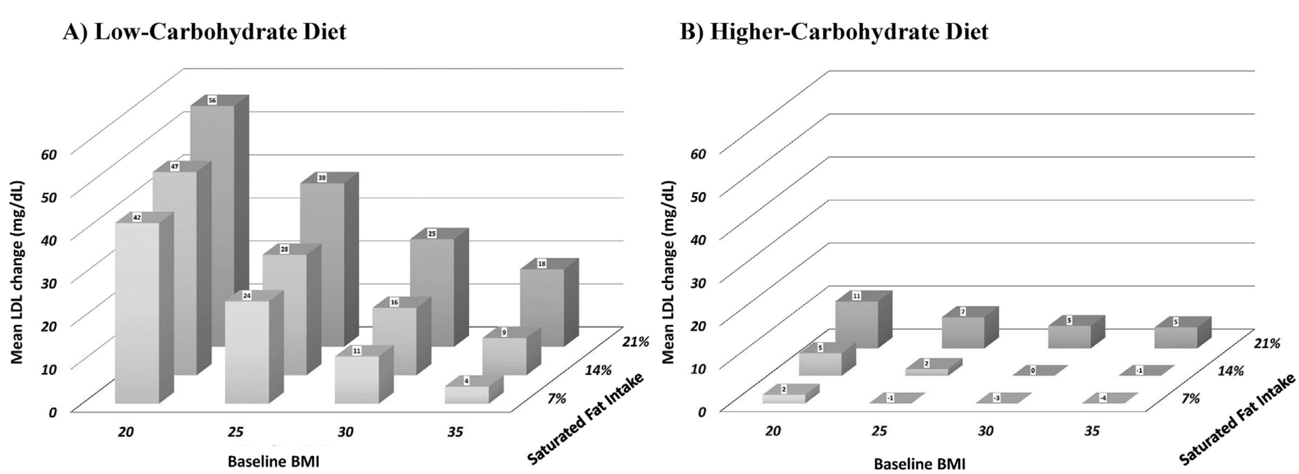

FIGURE 4. Joint associations of mean baseline BMI, saturated fat intake, and LDL cholesterol change using individual participant data. (A) Low-carbohydrate diet, $n = 328$. (B) Higher-carbohydrate diet, $n = 312$. Predictions from the model were drawn using a nonlinear orthogonal polynomial regression model. Saturated fat is expressed as a proportion of total energy intake. BMI (kg/m^2). BMI, body mass index; LDL, low-density lipoprotein.

conventional thinking that elevations in LDL cholesterol on an LCD, when they do occur, are primarily driven by increased saturated fat intake.

The Lipid Energy Model [4] provides a mechanistic explanation for the inverse relationship between BMI and LDL cholesterol change and the existence of the LMHR phenotype, involving the greater reliance on fat for metabolic fuel. According to this model, depletion of hepatic glycogen stores with carbohydrate restriction increases adipocyte lipolysis and resynthesis of triglycerides in the liver, which are exported in VLDL particles. Increased hepatic VLDL secretion, together with faster peripheral turnover of VLDL at adipose and lean tissues, yields a lipid profile characterized by low triglycerides, high HDL cholesterol, and high LDL cholesterol. On an LCD, this metabolic shift may be most pronounced in individuals with proportionately greater lean mass – facilitated by lower insulin resistance and a greater reduction in insulin and leptin concentrations – as inferred in part from studies of fasting (in which metabolic fuel oxidation shifts fully from carbohydrate to fat) [27–30]. Consistent with this mechanism, LDL cholesterol would also be expected to increase markedly on an LCD in individuals with high levels of physical activity, a prediction supported by observational evidence [31]. Interestingly, sodium-glucose transporter protein 2 inhibitors also shift metabolic fuel reliance from carbohydrate to fat (although typically to a lesser degree than an LCD) and raise LDL cholesterol [32]. Additional research will be needed to test the validity of this model.

The primary finding of our meta-analysis may reassure healthcare providers and patients contemplating the use of an LCD for the treatment of obesity-related diseases, including type 2 diabetes, as LDL cholesterol would not tend to increase despite high intakes of total and saturated fat. Conversely, LDL cholesterol can be expected to increase substantially among lean individuals adopting an LCD for other reasons, such as epilepsy and other neurological conditions, autoimmune disease, type 1 diabetes, or personal preference [33]. In these patients, LDL cholesterol should be monitored, and the potential risks compared with the benefits of an LCD weighed. However, the clinical significance of isolated LDL cholesterol elevation remains a topic of controversy. Changes in lipoprotein particle types with consumption of an LCD may confer lower risk than otherwise suggested by LDL cholesterol due in part to a proportionate decrease in small LDL particles and reduction in other lipid risk factors [triglycerides, HDL cholesterol, lipoprotein(a)] and to improvements in nonlipid risk factors (e.g., postprandial hyperglycemia, insulin resistance, chronic inflammation, hypertension) [34–38]. These beneficial effects of carbohydrate restriction may interact with or counterbalance any increase in total apolipoprotein B-containing particles. Indeed, several cohort studies found that individuals with isolated elevated LDL cholesterol, compared with those who also had high triglycerides and low HDL cholesterol, were at lower risk for coronary artery disease events and benefited less from statins [39,40]. In any event, for people who benefit from an LCD but experience a worrisome increase in LDL cholesterol, statin treatment could be considered.

Strengths of this meta-analysis include relatively large size [7–11], providing power to examine relationships with LDL cholesterol across a wide BMI range; long duration of several trials (e.g., 1 y), helping to exclude transient effects resulting from macronutrient changes; and use of IPD to confirm and extend the primary findings. Furthermore, as suggested by the high fail-safe-N and results of publication bias and sensitivity analyses, the findings appear robust.

One limitation of this study involves the possibility of bias among the original trials that inflate our estimate of the relationship between BMI and LDL cholesterol change. (Bias causing an underestimation of this relationship would not alter the clinical implications of the findings, considering their magnitude and strength.) Nonetheless, we think the results are generalizable because, for this to occur, the confounding factor(s) or methodological issues would need to be strongly associated with BMI and increasingly influential with greater BMI categories. Few other dietary factors or experimental conditions could plausibly affect LDL cholesterol to this degree (~50 mg/dL when comparing low compared with high BMI groups). Saturated fat, currently considered the most important dietary influence on LDL cholesterol, was observed to have a substantially lesser effect on LDL cholesterol than carbohydrate restriction in our models (including IPD). Differential cholesterol-lowering medication usage is another concern. However, baseline mean LDL cholesterol was not markedly elevated in the trials, suggesting a low likelihood that many individuals would spontaneously start this treatment during a trial; cholesterol-lowering drug use was specifically assessed in most of the trials; and our sensitivity analyses found similar results among trials that excluded any statin usage at baseline.

Another possible source of bias is differential adherence, such that studies of lean participants reduced carbohydrate intake to a substantially greater degree than those with high BMI participants, and methods to control for this possibility in the original trials were inadequate. However, we believe the possibility of this bias is remote for many reasons. First, per inclusion criteria, the trials used direct assessment of diet during the intervention. Therefore, for this bias to arise, not only would dietary adherence need to differ substantially based on BMI, but so would the accuracy of dietary reporting. Second, this differential adherence would need to have been so consistent among studies as to have caused absolute congruence within the low BMI category (all of which showed marked increases in LDL cholesterol) and also within the high BMI category (all of which showed a mean reduction in LDL cholesterol). Third, effect modification by BMI is also observed using IPD with comparable magnitude and direction across BMI subgroups. Fourth, the finding remains robust with the elimination of any single trial, including the largest one. Fifth, most of the trials in the high BMI category provide some objective biological evidence that the participants actually reduced carbohydrate intake (such as increased HDL cholesterol and decreased triglycerides, among other biomarkers reported). Sixth, 1 trial [41] in the highest BMI group used a feeding protocol in which fully prepared meals were provided to participants using state-of-the-art methods. This experimental approach reliably produces high dietary adherence (as biomarkers also show here). LDL cholesterol change in this trial [–4.0 (–8.6 to 0.6) mg/dL] was virtually the same as the overall LDL cholesterol change in the high BMI group [–6.7 (–12.1 to –1.3) mg/dL] and markedly different from the overall change in the low BMI group [+41.4 (19.6–63.3) mg/dL]. Seventh, the BMI effect modification is consistent with an a priori hypothesis based on physiological mechanisms.

Regarding other study limitations, 9 trials did not report saturated fat consumption (Table 1), somewhat diminishing our ability to compare the influence of this dietary factor with BMI on LDL cholesterol change. Related to this point, the comparative analyses were strongly influenced by 1 trial, DIETFITS, which had more participants than other trials included in the IPD combined. In DIETFITS, involving participants with BMI 28–40, both arms were advised to restrict saturated fat intake, whereas the other 2 trials contributing to IPD had lean participants and did not provide this advice. Thus, our IPD analyses may have underestimated the relative influence of saturated fat intake on LDL cholesterol change for people with obesity on an unrestricted LCD. However, in a recent large feeding study (not included in our sample because of a prerandomization run-in weight loss diet), LDL cholesterol did not differ on weight-maintenance diets with 20%, 40%, or 60% carbohydrate and 21%, 14%, and 7% saturated fat, respectively, after 20 wk among 147 participants with mean BMI of 32.4 [34]. Furthermore, our results are consistent with controlled feeding studies indicating a relatively small and nonlinear effect of saturated fat consumption on LDL cholesterol during carbohydrate restriction [41,42]. Change in body weight, a determinant of LDL cholesterol change, was variable among the trials. However, in our meta-regression, weight change was not a strong predictor of LDL cholesterol change (Table 1), and we included weight change as a covariate in our primary meta-analyses. Adjustment for weight change in the IPD analyses did not materially alter the results (Supplemental Figure 2). Finally, because comparisons were made across baseline BMI levels (i.e., without protection of randomization, which would be experimentally infeasible), BMI could be a marker, rather than mediator, of the observed relationships with LDL cholesterol change. Additional research will be needed to explore the causal mechanisms relating body composition to LDL cholesterol change.

In conclusion, our study demonstrates that much of the heterogeneity in LDL cholesterol response to an LCD is explained by BMI and highlights a novel phenotype, LMHR, susceptible to a large increase in this cardiovascular disease risk factor with carbohydrate restriction. These findings may allay concern for use of an LCD with a common clinical indication: treatment of obesity-related complications, including type 2 diabetes. Additional research will be needed to determine the clinical implications of LDL cholesterol increases with consumption of an LCD by lean patients for other indications.

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Author contributions

The authors' responsibilities were as follows – AS-M: designed the study, acquired and analyzed the data, conducted statistical analyses, and drafted the manuscript; YF-J, DF: designed the study, acquired and analyzed the data, and revised the manuscript; NGN: designed the study, acquired and analyzed the data, and drafted the manuscript; MAP: designed the study, acquired and analyzed the data, conducted statistical analyses, and revised the manuscript; GD: acquired and analyzed the data, conducted statistical analyses, and revised the manuscript; DSL: designed the study, acquired and analyzed the data, drafted the manuscript, obtained funding, and provided supervision, and all authors: read and approved the final manuscript.

Conflict of interest

DSL and NGN receive royalties for books that recommend a carbohydrate-modified diet. All other authors report no conflicts of interest. DSL is the Associate Editor of *The American Journal of Clinical Nutrition* and was not involved in the editorial evaluation of this manuscript.

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Data availability

The compiled data from the included studies, the data sets with anonymized individual patient data, and the code for reproducing both quantitative and graphical analyses will be available upon publication at https://github.com/AdrianSotoM/LMHR-LEM_SR-MAA.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajcnut.2024.01.009.

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