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RESEARCH

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Association of free-living diet composition with plasma lipoprotein(a) levels in healthy adults

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Abstract

Background Lipoprotein (a) [Lp(a)] is an apoB100-containing lipoprotein with high levels being positively associated with atherosclerotic cardiovascular disease. Lp(a) levels are genetically determined. However, previous studies report a negative association between Lp(a) and saturated fatty acid intake. Currently, apoB100 lowering therapies are used to lower Lp(a) levels, and apheresis therapy is FDA approved for patients with extreme elevations of Lp(a). The current study analyzed the association of free-living diet components with plasma Lp(a) levels.

Methods Dietary composition data was collected during screening visits for enrollment in previously completed lipid and lipoprotein metabolism studies at Columbia University Irving Medical Center via a standardized protocol by registered dietitians using 24 hour recalls. Data were analyzed with the Nutrition Data System for Research (Version 2018). Diet quality was calculated using the Healthy Eating Index (HEI) score. Fasting plasma Lp(a) levels were measured via an isoform-independent ELISA and apo(a) isoforms were measured using gel electrophoresis.

Results We enrolled 28 subjects [Black ($n=18$); Hispanic ($n=7$); White ($n=3$)]. The mean age was 48.3 ± 12.5 years with 17 males. Median level of Lp(a) was 79.9 nmol/L (34.4–146.0) and it was negatively associated with absolute (grams/day) and relative (percent of total calories) intake of dietary saturated fatty acids (SFA) (R = -0.43, $P=0.02$, SFA …(% CAL): R = -0.38, $P=0.04$), palmitic acid intake (R = -0.38, $P=0.05$), and stearic acid intake (R = -0.40, $P=0.03$). Analyses of associations with HEI score when stratified based on Lp(a) levels > or ≤ 100 nmol/L revealed no significant associations with any of the constituent factors.

Conclusions Using 24 hour recall, we confirm previous findings that Lp(a) levels are negatively associated with dietary saturated fatty acid intake. Additionally, Lp(a) levels are not related to diet quality, as assessed by the HEI score. The mechanisms underlying the relationship of SFA with Lp(a) require further investigation.

Keywords Lipoprotein(a), Diet quality, Dietary components, Saturated fatty acids, HEI

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Background

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death in the United States [1]. One independent and causal risk factor for developing ASCVD is high plasma level of lipoprotein(a) [Lp(a)] [2–4]. Lp(a) has two main protein components: an integral membrane protein, apolipoprotein (apo) B100, covalently bound to the glycoprotein apolipoprotein(a) [apo(a)] [2–4]. Plasma Lp(a) levels are 70–90% determined by the *LPA* gene [5–7]. Apo(a) varies in size from 300 to 800 kDa due to different numbers of Kringle 4 type 2 (KIV-2) repeats, ranging from 1 to > 40. A universal consensus for the threshold of elevated Lp(a) associated with ASCVD risk has not been determined [8], hence there are multiple different published cut-off ranges. However, a continuous causal association between Lp(a) and ASCVD is well established [9].

Lifestyle modifications, including exercise and diet interventions, are low-cost and effective ways to prevent and help treat cardiovascular disease. Lp(a) levels do not change or may slightly increase (10–15%) after intense exercise training in previously sedentary individuals [10, 11]. Additionally, unlike other apoB-containing lipoproteins and CVD risk factors (i.e. obesity, insulin resistance), in which diet modifications contribute to a decreased risk of events [12], Lp(a) levels do not change during cardio-beneficial diet interventions [13, 14]. Several studies have examined the possible effects of dietary interventions on Lp(a) [15–18]. Studies by Ginsberg et al. [18], Shin et al. [15], and Silaste et al. [16] observed a negative relationship between plasma Lp(a) levels and saturated fatty acids (SFA) [15, 16, 18]. Conversely, Haring et al. found a positive relationship between plasma Lp(a) levels and unsaturated fatty acids [17]. The studies suggest that overall diet composition may influence Lp(a) levels and may not be in line with diets that provide cardiovascular benefits. To date, none of the studies directly evaluate the relationship between the participants' free-living diet and Lp(a) levels prior to intervention, which may or may not have contributed to the results on saturated fat and Lp(a) levels observed. Additionally, these studies did not include apo(a) isoform size and race/ethnicity, both known to affect Lp(a) levels [19]. Therefore, we examined food records from a diverse cohort of subjects previously enrolled for studies that evaluated lipid and lipoprotein metabolism. We evaluated the relationship of Lp(a) levels with diet composition, and diet quality as measured by the Healthy Eating Index (HEI) score.

Methods

Study participants

All studies were approved by the Columbia University Irving Medical Center (CUIMC) institutional review board (IRB), and informed consent was obtained from all participants. Participants were healthy volunteers with no history of cardiovascular disease (CVD) or type 2 diabetes (T2D) and did not report taking any lipid-lowering medications [20, 21]. Dietary data were obtained from screening visits for enrollment in previously completed lipid and lipoprotein metabolism studies at CUIMC. Only individuals with complete dietary records were included in the present analysis [20, 21].

Study procedures

Participants were screened at our research center facilities after a 12 hour (hr) overnight fast. We recorded self-reported race/ethnicity (SRRE). Height and weight were measured using a scale, while wearing a hospital gown and no shoes. These measurements were used to calculate body mass index (BMI). Registered dietitians completed dietary 24 hr recalls, in person. Participants were excluded from this study if they followed non-conventional dietary habits such as the ketogenic diet or intermittent fasting. One dietary recall was obtained per participant via the multiple pass method [22, 23]. Dietary intake data were analyzed using Nutrition Data System for Research (NDSR) software Version 49 (2018) developed by the Nutrition Coordinating Center (NCC), University of Minnesota, Minneapolis, MN [24]. Diet macronutrient data were evaluated and included: carbohydrate, protein, and fat, including SFA, mono- (MUFA) and poly- (PUFA) unsaturated fatty acids as well as dietary fiber (soluble and insoluble). Diet composition was analyzed on an absolute [grams/day (g/d)] and relative basis [percent of total Calories (% Cal)]. This observational study examined the relationship of fasting Lp(a) levels with free-living diet composition, particularly fat intake.

Healthy eating index

Microsoft Excel was used to calculate the Healthy Eating Index (HEI) score 2015 for each participant. HEI-2015 describes the diet quality according to the recommendations outlined in the 2015–2020 Dietary Guidelines for Americans by generating a score from 0 to 100 (100 being 100% in congruence with the guidelines) [25]. The score is a composite of thirteen factors representing different food groups classically associated (positively or negatively) with chronic disease. The relationship between HEI score and Lp(a) level was evaluated in all subjects and in subgroups stratified by Lp(a) levels. There is no clinically accepted level to denote high Lp(a), therefore, we stratified our cohort into "high" and "low" using a cut point that considers two published recommendations for Lp(a) levels ("high"—> 100 nmol/L; "low"—≤ 100 nmol/L). The National Heart, Lung, and

Blood Institute (NHLBI) Working Group Recommendations use Lp(a) levels > 75 nmol/L as "high" [26], and the 2019 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) Guidelines consider elevated Lp(a) levels as Lp(a) ≥ 125 nmol/L [27].

Laboratory measurements

Each participant had a 12-hr fasting blood draw via an intravenous (IV) catheter from forearm veins. Briefly, blood was obtained in EDTA containing test tubes, immediately placed on ice, and spun in a centrifuge at 1693 rotational centrifugal force, 4° Celsius (C) for 20 min. Plasma was isolated from the test tube and stored in a -80° C freezer. Frozen samples were shipped on dry ice to the laboratory of Dr. Santica Marcovina (Seattle, Washington), where plasma Lp(a) levels were measured using an isoform-independent, double monoclonal antibody-based enzyme-linked immunosorbent assay (ELISA) [28–30]. Lp(a) levels were not normally distributed, so we calculated medians and interquartile range (IQR). Apo(a) isoform size measurements were performed by the same laboratory [31], which is currently the best available method as not all genetically determined isoforms of apo(a) are expressed and can be found in circulation as an Lp(a) particle. Plasma lipids (total cholesterol (TC), triglycerides (TG), and high-density lipoprotein (HDL) cholesterol) were measured by Integra400plus (Roche). Plasma low-density lipoprotein (LDL) cholesterol (C) levels were estimated using the Friedewald formula. Plasma apoB100 was measured using ELISA kit # 3715-1HP-2 from Mabtech, Inc, Cincinnati, OH.

Weighted Isoform Size (wIS) calculations

Most individuals express two apo(a) isoforms in plasma that vary in size, the smaller isoforms are dominant and inversely correlated with Lp(a) plasma levels. To account for the difference in percent expression (determined by gel electrophoresis) of each isoform, we calculated a weighted isoform size [32]. Example: If the two allele sizes are 20 and 30, with relative expression of 70% and 30%, respectively, the *wIS* is 0.7*20 + 0.3*30 = 23.

Statistical analysis

Based on previously identified relationships of diet components with lipids, twenty-three dietary variables were identified a priori for analysis from the 170 variables available via NDSR output. Diet data are presented as absolute (g/d) and relative (% Cal) intake. Pearson correlation and linear regression were used to evaluate relationships between variables using the R software [33]. Apo(a) isoform size and SRRE are determinants of plasma Lp(a) levels [19], as such we control for these variables in our linear regression models. Unpaired t-test was used to analyze HEI score differences by stratifying subjects into two Lp(a) groups (≤ 100 nmol/L and > 100 nmol/L). Statistical significance was set at a *P*-value less than or equal to 0.05.

Results

Twenty-eight participants met the inclusion criteria for the study. Baseline characteristics including lipid and lipoprotein levels are listed in Table 1. The mean age of the cohort was 48.3 ± 12.5 years; 17 out of the 28 subjects were male and 18 listed Black as their SRRE. The participants were overweight with a mean BMI of 29.5 ± 3.3 kg/m^2. Plasma lipid levels (TC, TG, HDL-C, LDL-C) and apoB100 levels were within normal ranges. The median Lp(a) level was 79.9 nmol/L (IQR 34.4—146 nmol/L) and the calculated *wIS* was 22.4. As observed in larger published cohorts, apo(a) isoform size was negatively associated with Lp(a) levels (Supplemental Fig. 1). Individual Lp(a) levels, isoform size expressed, and calculated *wIS* for the full cohort are presented in Supplemental Table 1.

Relationships between dietary components—plasma lipids, lipoproteins and Lp(a)

As expected, apoB100 levels were positively and significantly correlated with absolute and relative values of total fat and particularly absolute and relative intake of SFA. (Table 2).

Table 1 Participant characteristics (*n* = 28)

Sex n(%)	
Male	17 (60.7)
Race/Ethnicity n(%)	
Black	18 (64.3)
Hispanic	7 (25.0)
White	3 (10.7)
Age (years)	48.3 ± 12.5
BMI (kg/m^2)	29.5 ± 3.3
Total Cholesterol (mg/dL)	152.8 ± 22.3
Total Triglyceride (mg/dL)	98.5 ± 43.6
LDL-C (mg/dL)	86.6 ± 18
HDL-C (mg/dL)	46.6 ± 12.8
ApoB100 (mg/dL)	90.7 ± 27.2
Lp(a) (nmol/L)	79.9 (34.4–146.0)
Apo(a) *wIS*	22.4 ± 4.6
HEI score	57.1 ± 16

Data are presented as mean ± SD, median (IQR), or n (%)

BMI Body Mass Index, *LDL-C* Low-Density Lipoprotein Cholesterol, *HDL-C* High-Density Lipoprotein Cholesterol, *ApoB100* Apoprotein (B100), *Lp(a)* Lipoprotein (a), *Apo(a)* Apoprotein (a), *HEI* Healthy Eating Index, *n* number, *kg* kilogram, *m2* meter squared, *mg* milligrams, *dL* deciliter, *IQR* Interquartile Range, *SD* Standard Deviation

Table 2 Relationship between Apo lipoprotein B100 and dietary factors

	Absolute		Relative	
	R	*P*-value	R	*P*-value
Total Fat	0.40	0.036*	0.52	0.005*
SFA	0.58	0.001*	0.62	< 0.001*

SFA Saturated fatty acid

* - significant *P*-value of ≤ 0.05

Relationship of Lp(a) with macronutrients

The mean intakes of absolute and relative total carbohydrate, protein, and fat in our participants can be seen in Table 3. We found no relationship between average energy intake (kcal/d) and Lp(a) concentration (R = -0.32, *P* = 0.10). A moderate negative relationship was observed between fat intake (g/d) and Lp(a) levels (*P* = 0.08), but this relationship did not persist when normalized to percent of total calories (*P* = 0.13). We observed no relationships between plasma Lp(a) levels and carbohydrate or protein intake (Table 3). However, when we included *wIS* and SRRE in our model we observed a positive trend between Lp(a) and relative intake of carbohydrates (*P* = 0.07) and a negative relationship between fat (*P* = 0.05) and Lp(a) levels (Table 3).

Effects of saturated fatty acids—palmitic acid and stearic acid on Lp(a)

The mean intakes of absolute and relative amounts of SFA, palmitic acid, and stearic acid intake are reported in Table 3. There was an inverse relationship between Lp(a) levels with dietary SFA [absolute (R = -0.43, *P* = 0.02) and relative (R = -0.38, *P* = 0.04) (Fig. 1A)], dietary palmitic acid [absolute (R = -0.38, *P* = 0.05) (Fig. 1B)], and dietary stearic acid [absolute (R = -0.40, *P* = 0.03) (Fig. 1C)]. These relationships persisted when controlling for *wIS* and SRRE. Extrapolation of these findings suggest that for every one percent increase in calories from SFA, Lp(a) levels decrease by 5.97 nmol/L. We also observed trends toward a negative correlation between Lp(a) and relative intake of palmitic (R = -0.33, P = 0.08) and stearic acid (R = -0.37, P = 0.06).

Effects of unsaturated fatty acids—monounsaturated fatty acids and polyunsaturated fatty acids on Lp(a) levels

The mean absolute and relative values of total MUFA, palmitoleic acid, and oleic acid intake in our population are listed in Table 3. The average daily PUFA, linoleic acid, and linolenic acid intake are also reported in Table 3. Plasma Lp(a) levels were not associated with absolute (g/d) or relative (% calories) MUFA or PUFA intake, even when adjusted for *wIS* and SRRE.

Table 3 Relationship between dietary variables and Lp(a)

Dietary Variables		Absolute Intake			Relative Intake			Absolute Intake[a]		Relative Intake[a]	
		Mean ± SD g/d	R	*P*-value	Mean ± SD % Cal	R	*P*-value	R^2	*P*-value	R^2	*P*-value
Total Energy	**kcal/d**	1722.6 ± 599.8	-0.32	0.1	NA	NA	NA	0.46	0.203	NA	NA
Macronutrients	Carbohydrate	221.8 ± 87.7	-0.18	0.35	50.7 ± 12.5	0.24	0.22	0.42	0.617	0.5	0.07
	Protein	79.5 ± 35.9	-0.27	0.17	18.5 ± 5.8	0.03	0.90	0.47	0.156	0.42	0.66
	Fat	60.5 ± 29.9	-0.34	0.08	30.5 ± 11.7	-0.29	0.13	0.48	0.108	0.51	0.05
Saturated Fatty Acids	Total SFA	18.1 ± 10.8	-0.43	0.02*	9.2 ± 4.9	-0.38	0.04*	0.52	0.04*	0.53	0.03*
	Palmitic Acid	10.6 ± 6	-0.38	0.05*	7.7 ± 4.1	-0.33	0.08	0.52	0.047*	0.53	0.03*
	Stearic Acid	4.4 ± 3.1	-0.4	0.03*	2.3 ± 1.4	-0.37	0.06	0.52	0.036*	0.54	0.02*
Unsaturated Fatty Acids	Total MUFA	22.8 ± 13.1	-0.14	0.47	11.4 ± 5.5	-0.09	0.66	0.43	0.529	0.43	0.54
	Palmitoleic Acid	1.2 ± 0.9	-0.26	0.18	0.6 ± 0.5	-0.17	0.4	0.44	0.308	0.43	0.44
	Oleic Acid	20.9 ± 12.2	-0.13	0.51	10.6 ± 5.1	-0.08	0.7	0.43	0.55	0.43	0.56
	Total PUFA	14.1 ± 8.9	-0.26	0.18	7.1 ± 3.3	-0.18	0.37	0.47	0.152	0.47	0.14
	Linoleic Acid	12.0 ± 8.2	-0.25	0.20	6.1 ± 3.1	-0.18	0.37	0.47	0.149	0.47	0.13
	Linolenic Acid	1.4 ± 0.7	-0.37	0.05	0.71 ± 0.3	-0.25	0.19	0.49	0.092	0.46	0.19
Dietary Fiber[b]	Soluble Fiber	6.3 ± 4.2	-0.08	0.67	3.69 ± 1.85	0.1	0.6	0.43	0.466	0.42	0.91
	Insoluble Fiber	15.4 ± 11.3	-0.09	0.64	8.95 ± 6.31	0.02	0.92	0.43	0.48	0.46	0.19

SD Standard deviation. Pearson correlation was used to evaluate the relationships between variables. *d* day, *g* grams, *Kcal* kilocalories, *NA* Not Applicable

[a] Linear regression was used to evaluate the relationships between variables, while controlling for wIS and SRRE. wIS, weighted Isoform Size; SRRE, Self-Reported Race/Ethnicity

* - significant P-value of ≤ 0.05

[b] —Relative intake values are calculated as % calories using g/1000 cal

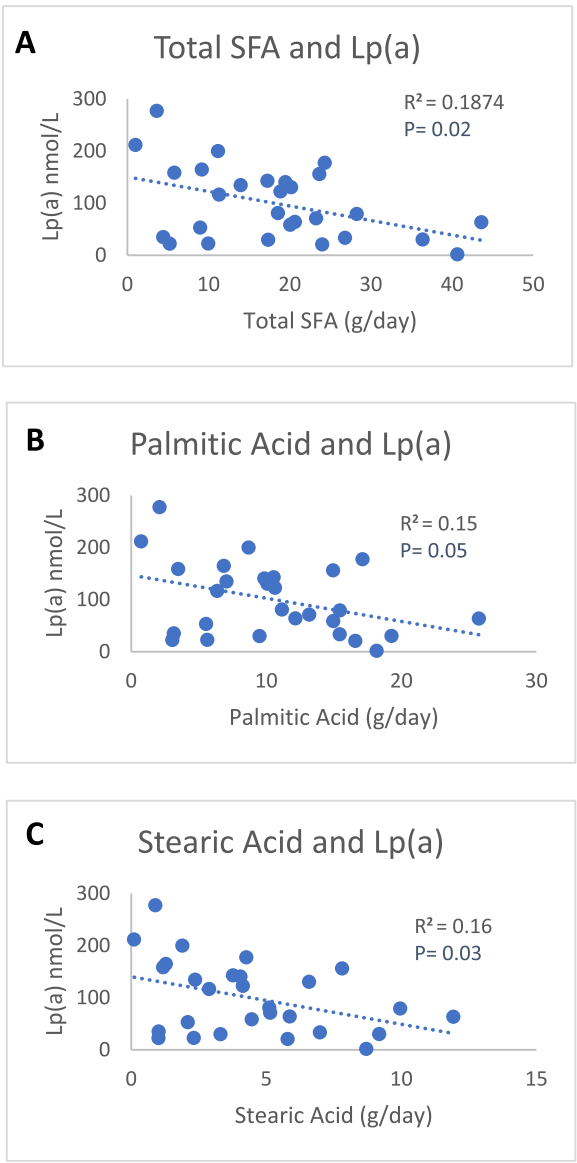

Fig. 1 Title: Relationship between Saturated Fatty Acids, Palmitic Acid, Stearic Acid and Lp(a). Legend: Scatter plot of percent calories from SFA (**A**), Palmitic acid (**B**) and Stearic Acid (**C**) with Lp(a) with a best fitted line. Pearson correlation was done to obtain the p-value. SFA, Saturated Fatty Acid; Lp(a), lipoprotein(a) Alpha significance set at $p \leq 0.05$

Effects of dietary fiber on Lp(a) levels

The mean soluble and insoluble fiber intake values are reported in Table 3, and there were no significant relationships with Lp(a) even after adjusting for *wIS* and SRRE.

Relationships of Lp(a) with healthy eating index score

Our cohort had an average HEI score of 57.1 ± 16, this is similar to results published by National Health and Nutrition Examination Survey (NHANES), which found the average HEI score for Americans is 58 [34], suggesting that our sample reflects dietary patterns previously described throughout the USA population. The score calculation is made of 13 food components, which we graphically represent for our cohort in Fig. 2A. An HEI score of 100 would suggest perfect alignment with the dietary guidelines. We investigated the relationship between our cohort's HEI index score and Lp(a) levels (Fig. 3).

There was no statistically significant relationship between HEI score and Lp(a) level (Fig. 3) even after adjusting for *wIS* and SRRE ($P=0.13$). We examined whether this relationship varied in individuals with high versus low Lp(a) level but found no differences between the groups ($P=0.09$) (Table 4). Further, when analyzed for each of the thirteen dietary subgroups that make up the HEI score by unpaired t-test between low and high Lp(a) (Fig. 2B), only dietary saturated fat reached statistical significance ($P=0.03$).

Discussion

The current study aimed to evaluate the relationships between a free-living diet and Lp(a) plasma levels. These relationships had been studied in controlled settings (randomized studies), yet we wanted to see if the previous reports were also found in free-living environments. Our study population was small, however the small group showed similar positive relationships between plasma apoB100 levels and TC (R = 0.41, $P=0.03$), and LDL-C (R = 0.52, $P=0.005$) which have been found in larger cohorts, validating the relationship of apoB100 with plasma lipids. Moreover, they showed positive relationships between plasma apoB100 with dietary total fat and SFA, validating the previously relationships between diet and lipoproteins in this small cohort [35].

Plasma Lp(a) levels are strongly determined by genetics [5–7], and high levels of Lp(a) are a causal risk factor for ASCVD [31]. Heart healthy diets and lifestyle changes are the first steps to decreasing cardiovascular risk [14], yet these have not been shown to lower Lp(a) levels.

Previous results from the OMNI study showed a significant increase in Lp(a) levels with different macronutrient rich controlled diets [change in Lp(a) mean from baseline (*P*-value): carbohydrate + 3.2 (< 0.001); protein + 4.7 (< 0.001); unsaturated fat + 2.1(< 0.001)] [17]. However, in our data set controlling for *wIS* and race, we find no correlations between Lp(a) levels and protein or unsaturated fat, and a positive trend with relative intake of carbohydrates.

Current Dietary Guidelines for Americans (2020–2025) recommend consuming less than 10% of daily calories from saturated fat [36]. The current study supports

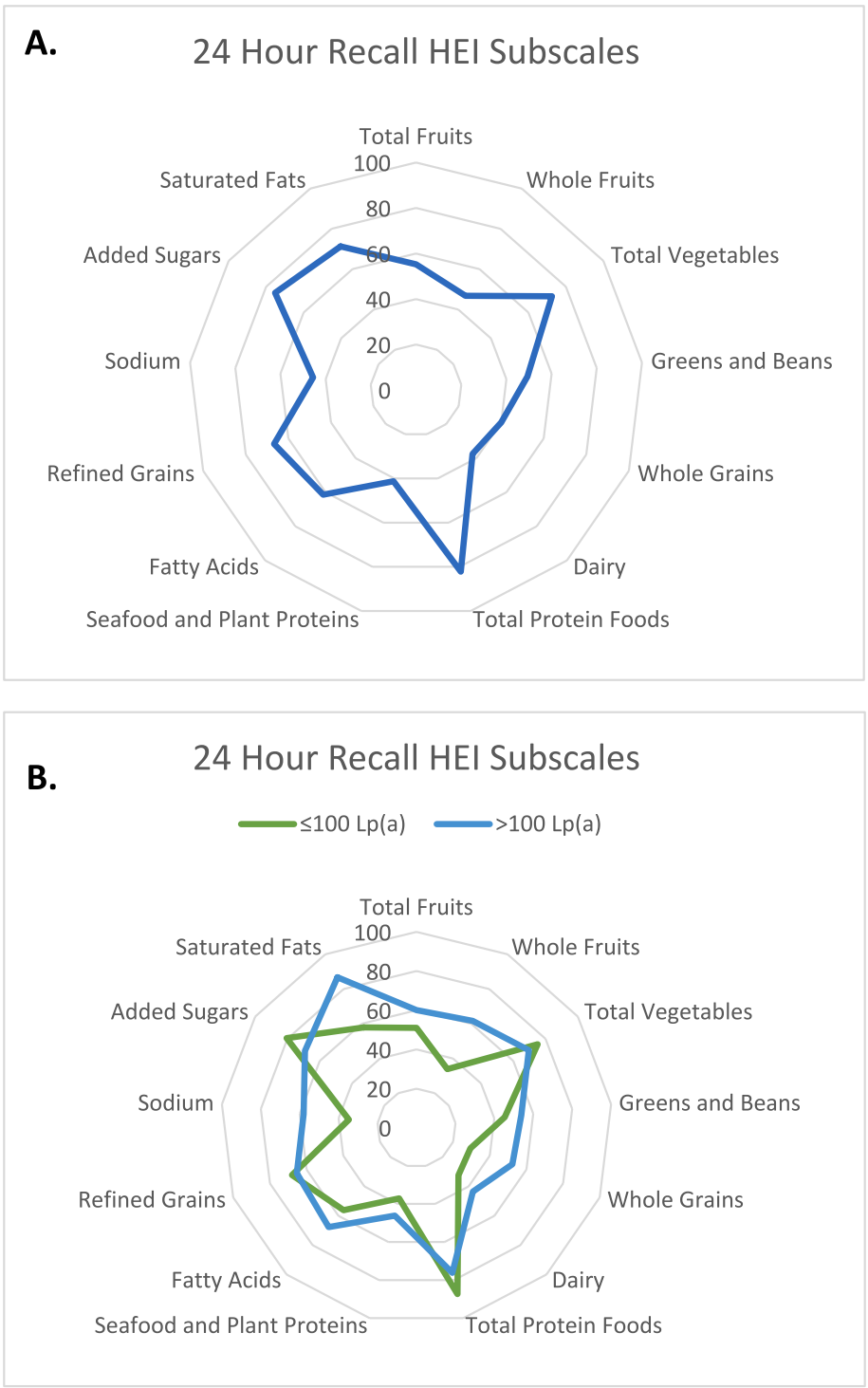

Fig. 2 Radar Plots for Healthy Eating Index Broken Down by Food Groups **A**. Overall HEI assessment based on individual food groups that make up HEI score. **B**. Unpaired t-test, presenting the relationships between high and low Lp(a) levels with whole fruits (P = 0.10), sodium (*P* = 0.14), whole grains (*P* = 0.15), saturated fats (*P* = 0.03). HEI, Healthy Eating Index; Lp(a), Lipoprotein(a) Alpha significance set at $P < 0.05$

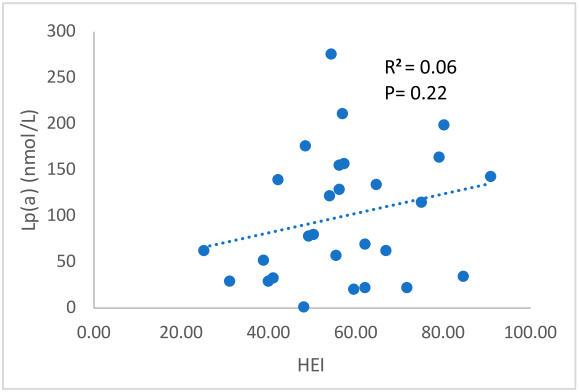

Fig. 3 Relationship between Lp(a) and HEI. Lp(a): Lipoprotein(a); HEI: Healthy Eating Index

Table 4 Relationship between HEI score and Lp(a) value stratified by normal and high Lp(a) levels ($N=28$)

	HEI Score Mean ± SD	*P*-value
Lp(a) Value-Low ≤ 100 nmol/L ($n=15$)	52.4 ± 16	0.09
Lp(a) Value-High > 100 nmol/L ($n=13$)	62.6 ± 14.2	

Unpaired t-test was used to evaluate the relationships between variables

HEI Healthy Eating Index, *SD* Standard Deviation

Alpha significance set at P ≤ 0.05

previous findings from controlled diet studies that show high SFA content associates with lower levels of Lp(a) [15, 16, 18]. Using the average and standard deviation of SFA intake observed in our cohort (9.2 ± 4.9% Cal) and our linear regression model which includes *wIS* and SRRE, we estimate that an individual with an Lp(a) level of 100 nmol/L in whom SFA intake increases, for example, from 4 to 9%, will experience a decrease in their Lp(a) level to 70.13 nmol/L.

Our data on free-living diets can be compared to controlled studies such as the Delta study. In that study, three different controlled diet compositions were investigated [average American diet (AAD) (37% Fat, 16% SFA, 14% MUFA, 7% PUFA); step-1 diet (30% Fat, 9% SFA, 14% MUFA, 7% PUFA); low saturated fat diet (Low Sat) (26% Fat, 5% SFA, 14% MUFA, 7% PUFA)] and Lp(a) levels decreased as the percent of SFA of total calories was increased [AAD: (%kcal SFA = 15.0 ± 0.4, Lp(a) = 15.5 ± 1.8 mg/dL); step-1: (%kcal SFA = 9.0 ± 0.1, Lp(a) = 17.0 ± 1.8 mg/dL); low sat: (%kcal SFA = 6.1 ± 0.5, Lp(a) = 18.2 ± 1.9 mg/dL)] [18]. Two additional studies, one by Shin et al. observed Lp(a) increases similar to those observed in Delta study as participants switched from a high fat/low carb diet (40% Fat, 13% SFA, 11% MUFA, 13.8% PUFA, 3.4% trans-fat, 45% carbohydrate, 15% protein) to a low fat/high carb diet (20% Fat, 4.9% SFA, 9.9% MUFA, 5.1% PUFA, 2.4% trans-fat, 65% carbohydrate, 15% protein), from an Lp(a) level of 8.91 (IQR 3.41 – 34.6) mg/dL to 11.47 (IQR 3.84 – 38.78) mg/L, respectively. Silaste et al. examined how dietary fat and vegetable consumption affected lipid levels. Using baseline measurements and two separate diets [baseline (36 ± 6 percent of total energy intake (E%) from fat, 15 ± 3 E% SFA, 14 ± 3 E% MUFA, 6 ± 1 E% PUFA, 46 ± 7 E% carbohydrate, 17 ± 2 E% protein), low fat with low vegetable (LFLV) consumption (31 E% fat, 11 E% SFA, 13 E% MUFA, 7 E% PUFA, 49 E% carbohydrate, 20 E% protein) and low fat with high vegetable (LFHV) consumption (31 E% fat, 9.5 E% SFA, 11 E% MUFA, 9.5 E% PUFA, 50 E% carbohydrate, 20 E% protein)], the authors found that Lp(a) levels increased by 7% from baseline to LFLV diet and 9% from baseline to LFHV diet. More recently, a study by Ebbeling et al., showed that Lp(a) levels went down significantly (14.7%) when subjects consumed a low carbohydrate, high fat diet (60% of total energy from fat, 21% SFA, 25% MUFA, 11% PUFA, 20% carbohydrate, 20% protein) [37] compared to moderate-carbohydrate diet (40% of total energy from fat, 14% SFA, 16% MUFA, 9% PUFA, 40% carbohydrate, 20% protein) and high-carbohydrate diet (20% of total energy from fat, 7% SFA, 8% MUFA, 5% PUFA, 60% carbohydrate, 20% protein), where Lp(a) decreased by 2.1% and increased by 0.2% without significance, respectively. A similar observation was recently described in the GET-READI, randomized crossover feeding study. In this study conducted in African American population, participants either consumed the American diet with 16% SFA or dietary approaches to stop hypertension (DASH) diet with 6% SFA, for 5 weeks. Lp(a) levels were 44 mg/dl on the 16% SFA diet and 58 mg/dL with the 6% SFA diet [38]. However, in another study, where participants consumed frozen plant-based meals for 5 weeks during Lent (SFA 4.7% Kcal), researchers observed a significant reduction in Lp(a) by 10% (from 56 to 51 mg/dL) [39]. The differences in the findings reported in the latter study could be due to presence of hypertension and diabetes in the study subjects as the previous studies reported findings in otherwise healthy populations.

Our findings show a higher effect size (by a factor of 6 to 8) compared to the Delta study and the other two crossover studies (Shin, Silaste) (Supplemental Fig. 2). One reason can be our small cohort and the cross-sectional nature of the study. However, our ability to replicate effects of SFA on Lp(a) in free-living environments highlights its role in regulating Lp(a) levels. However, the possibility of one or two outliers influencing the

regression coefficient in our small cohort fitted with two continuous variables (*wIS*, SFA%) and three SRRE categories is real. When we looked further into intercorrelations among the predictor variables that we examined, we found that SFA% was negatively correlated with *wIS* and was higher in Blacks compared to the other two SRRE groups. With our current knowledge, these relationships have no biological basis and could have arisen by chance. Since the SFA% was significantly correlated with Lp(a) level only in the presence of *wIS* and SRRE and both correlated separately with SFA%, we would like to be conservative and conclude that the effect of SFA% on Lp(a) level is negative, while the magnitude of the effect may be overestimated due to the small cohort. The three crossover studies (Delta, Shin, Silaste) do not have this concern since each subject was studied at different SFA% levels, and so each subject served as their own control.

The current study adds another body of evidence, including apo(a) isoform size and SRRE, that support higher SFA diets associated with low Lp(a) levels. Neither our study nor previous studies have performed metabolic studies that could help elucidate the mechanisms that are regulating these reported associations. We hypothesize that the lower Lp(a) levels with diets high in SFA could be due to decreased production of Lp(a) particles.

A mechanism for this relationship could be that SFA intake changes the fatty acid profile in the phospholipid membrane of an apoB100-containing particles in the liver (main protein that binds to apo(a) in the liver) and thereby regulates the synthesis and secretion of Lp(a) particles. There are no data reported for understanding the effects of macronutrients on synthesis or production of Lp(a) particles.

Another mechanism proposed by Enkhmaa et al., suggest that lower SFA diets could reduce the clearance of Lp(a) particles via the LDL receptor (LDLr) [40]. This could be attributable to increased competition with other apoB100 containing particles, including LDL. SFA have been shown to interfere with the formation of cholesterol esters and through accumulation of cholesterol preventing activation of the sterol receptor binding protein which can downregulate LDLr which has been proposed as one of the mechanisms whereby Lp(a) particles can get cleared [41]. A recent study from our group showed that both production and clearance of Lp(a) and isoforms regulate its level [32]. Therefore, we speculate that diet composition may be regulating Lp(a) levels through combined mechanisms.

Study strengths and limitations

Although a small study, our calculated diet quality based on HEI analysis is similar to those reported in larger cohort studies [34]. The HEI score provides a way to assess diet quality, and we hypothesized that a higher HEI score (better overall diet quality) would correlate with a lower level of Lp(a). However, we found no significant relationship between HEI and Lp(a) levels including saturated fat. Importantly, when stratified by Lp (a)level ($\leq$ or $>$ 100 nmol/L), we observed a statistically significant relationship with saturated fat that makes up the HEI score. The low Lp(a) group had a lower score for saturated fat (58%) [compared to high (87%)], meaning they consumed more saturated fat and thus received a lower score when HEI was calculated [25]. This data supports our overall findings on the negative relationship of SFA with Lp(a) levels.

Our study has several limitations: (1) we had a small sample size based on availability of complete food records and low enrollment numbers that are needed to complete our metabolic studies, and (2) the study was observational in nature. There are known limitations to 24-hr dietary intake data such as recall bias, which may be skewed based on the subject's desire to express their intake to the recorder. It is possible that participants under or over-reported various foods or left out stereotypically undesirable foods entirely. Photographic or meal-logging systems could have been used to help minimize this bias, however these dietary assessment tools may impart additional bias as participants may consciously or subconsciously change their intake whenever diet information is collected. Additionally, only one recall per participant was analyzed for this study. Despite these limitations, the study population did have similar SFA intake compared to larger controlled randomized diet studies that have similar findings.

Conclusion

Our findings support that increased dietary saturated fat is associated with low Lp(a) levels. However, the mechanisms regulating these relationships need to further be investigated as diets high in SFA have been linked to adverse cardiovascular risk. Together with the growing field of nutrigenomics [42], it is possible that individualized diet recommendations can be tailored to address a patient's ASCVD risk profile, and determine what is best for individuals with high levels of Lp(a).

Abbreviations

ASCVD	Atherosclerotic cardiovascular disease
[Lp(a)]	Lipoprotein(a)
apo	Apolipoprotein
[apo(a)]	Apolipoprotein(a)
KIV-2	Kringle 4 type 2
SFA	Saturated fatty acids
HEI	Healthy Eating Index
IRB	Institutional review board
CVD	Cardiovascular disease
T2D	Type 2 diabetes
CUIMC	Columbia University Irving Medical Center

SRRE	Self-reported race/ethnicity
BMI	Body mass index
NDSR	Nutrition Data System for Research
NCC	Nutrition Coordinating Center
MUFAs and PUFAs	Mono-and poly- unsaturated fatty acids
NHLBI	National Heart, Lung, and Blood Institute
ESC	European Society of Cardiology
EAS	European Atherosclerosis Society
IV	Intravenous
IQR	Interquartile ranges
TC	Total cholesterol
TG	Triglycerides
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
ELISA	Enzyme-linked immunosorbent assay
wIS	Weighted isoform size
LFLV	Low fat with low vegetable
LFHV	Low fat with high vegetable
DASH	Dietary Approaches to Stop Hypertension
NHANES	National Health and Nutrition Examination Survey
NCEP ATP	The National Cholesterol Education Program Adult Treatment Panel
AHA	American Heart Association
TLC	Therapeutic lifestyle changes

Supplementary Information

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Additional file 1.

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Authors' contributions
A.M., R.R., H.S., and G.R.-S. data analysis; A.M., N.M., K.K., H.S., T.T., and G.R.-S. investigation; K.K., A.M, H.S., G.R.-S. writing-original draft preparation; N.M., A.M., G.R.-S. visualization; N.M., R.R., and T.T. G.R.-S. reviewing and editing; G.R.-S. conceptualization; G.R.-S. methodology; G.R.-S. supervision; G.R.-S. funding; G.R.-S. resources.

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Availability of data and materials
The datasets generated during and/or analyzed during the current study are available in the LabArchives upon request.

Declarations

Ethics of approval and consent to participate
All studies were approved by the CUIMC institutional review board (IRB), and informed consent was obtained from all participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Heron M. Deaths: leading causes for 2016. Natl Vital Stat Rep. 2018;67(6):1–77.
2. Berg K. A new serum type system in man-the LP system. Acta Pathology Microbiology Scandanavia. 1963;59:369–82.
3. Schmidt K, Noureen A, Kronenberg F, Utermann G. Structure, function, and genetics of lipoprotein (a). J Lipid Res. 2016;57(8):1339–59.
4. Boerwinkle E, Leffert CC, Lin J, Lackner C, Chiesa G, Hobbs HH. Apolipoprotein(a) gene accounts for greater than 90% of the variation in plasma lipoprotein(a) concentrations. J Clin Invest. 1992;90(1):52–60.
5. Kassner U, Schlabs T, Rosada A, Steinhagen-Thiessen E. Lipoprotein(a)–An independent causal risk factor for cardiovascular disease and current therapeutic options. Atheroscler Suppl. 2015;18:263–7.
6. Nordestgaard BG, Langsted A. Lipoprotein (a) as a cause of cardiovascular disease: insights from epidemiology, genetics, and biology. J Lipid Res. 2016;57(11):1953–75.
7. Tsimikas S, Hall JL. Lipoprotein(a) as a potential causal genetic risk factor of cardiovascular disease: a rationale for increased efforts to understand its pathophysiology and develop targeted therapies. J Am Coll Cardiol. 2012;60(8):716–21.
8. Varvel S, McConnell JP, Tsimikas S. Prevalence of elevated Lp(a) mass levels and patient thresholds in 532 359 patients in the United States. Arterioscler Thromb Vasc Biol. 2016;36(11):2239–45.
9. Kronenberg F, Mora S, Stroes ESG, Ference BA, Arsenault BJ, Berglund L, et al. Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement. Eur Heart J. 2022;43(39):3925–46.
10. Mackinnon LT, Hubinger LM. Effects of exercise on lipoprotein(a). Sports Med. 1999;28(1):11–24.
11. Hubinger L, Mackinnon LT, Lepre F. Lipoprotein(a) [Lp(a)] levels in middle-aged male runners and sedentary controls. Med Sci Sports Exerc. 1995;27(4):490–6.
12. Ernst ND, Cleeman JI. National cholesterol education program keeps a priority on lifestyle modification to decrease cardiovascular disease risk. Curr Opin Lipidol. 2002;13(1):69–73.
13. Skulas-Ray AC, Wilson PWF, Harris WS, Brinton EA, Kris-Etherton PM, Richter CK, et al. Omega-3 fatty acids for the management of hypertriglyceridemia: a science advisory from the American heart association. Circulation. 2019;140(12):e673–91.
14. Pallazola VA, Davis DM, Whelton SP, Cardoso R, Latina JM, Michos ED, et al. A clinician's guide to healthy eating for cardiovascular disease prevention. Mayo Clin Proc Innov Qual Outcomes. 2019;3(3):251–67.
15. Shin MJ, Blanche PJ, Rawlings RS, Fernstrom HS, Krauss RM. Increased plasma concentrations of lipoprotein(a) during a low-fat, high-carbohydrate diet are associated with increased plasma concentrations of apolipoprotein C-III bound to apolipoprotein B-containing lipoproteins. Am J Clin Nutr. 2007;85(6):1527–32.
16. Silaste ML, Rantala M, Alfthan G, Aro A, Witztum JL, Kesaniemi YA, et al. Changes in dietary fat intake alter plasma levels of oxidized low-density lipoprotein and lipoprotein(a). Arterioscler Thromb Vasc Biol. 2004;24(3):498–503.
17. Haring B, von Ballmoos MC, Appel LJ, Sacks FM. Healthy dietary interventions and lipoprotein (a) plasma levels: results from the Omni Heart Trial. PLoS ONE. 2014;9(12): e114859.
18. Ginsberg HN, Kris-Etherton P, Dennis B, Elmer PJ, Ershow A, Lefevre M, et al. Effects of reducing dietary saturated fatty acids on plasma lipids and lipoproteins in healthy subjects: the DELTA Study, protocol 1. Arterioscler Thromb Vasc Biol. 1998;18(3):441–9.
19. Patel AP, Wang M, Pirruccello JP, Ellinor PT, Ng K, Kathiresan S, et al. Lp(a) (Lipoprotein[a]) concentrations and incident atherosclerotic

cardiovascular disease: new insights from a large national biobank. Arterioscler Thromb Vasc Biol. 2021;41(1):465–74.
20. Nandakumar R, Matveyenko A, Thomas T, Pavlyha M, Ngai C, Holleran S, et al. Effects of mipomersen, an apolipoprotein B100 antisense, on lipoprotein (a) metabolism in healthy subjects. J Lipid Res. 2018;59(12):2397–402.
21. Thomas T, Zhou H, Karmally W, Ramakrishnan R, Holleran S, Liu Y, et al. CETP (Cholesteryl Ester Transfer Protein) inhibition with anacetrapib decreases production of Lipoprotein(a) in mildly hypercholesterolemic subjects. Arterioscler Thromb Vasc Biol. 2017;37(9):1770–5.
22. Conway JM, Ingwersen LA, Moshfegh AJ. Accuracy of dietary recall using the USDA five-step multiple-pass method in men: an observational validation study. J Am Diet Assoc. 2004;104(4):595–603.
23. Conway JM, Ingwersen LA, Vinyard BT, Moshfegh AJ. Effectiveness of the US Department of Agriculture 5-step multiple-pass method in assessing food intake in obese and nonobese women. Am J Clin Nutr. 2003;77(5):1171–8.
24. Schakel SF. Maintaining a nutrient database in a changing marketplace: keeping pace with changing food products—a research perspective. J Food Compos Anal. 2001;14(3):315–22.
25. Krebs-Smith SM, Pannucci TE, Subar AF, Kirkpatrick SI, Lerman JL, Tooze JA, et al. Update of the healthy eating index: HEI-2015. J Acad Nutr Diet. 2018;118(9):1591–602.
26. Tsimikas S, Sergio F, Ferdinand KC, Ginsberg HN, Koschinsky ML, Marcovina SM, et al. NHLBI working group recommendations to reduce Lipoprotein(a)-mediated risk of cardiovascular disease and aortic stenosis. J Am Coll Cardiol. 2018;71(2):177–92.
27. Roeseler E, Julius U, Heigl F, Spitthoever R, Heutling D, Breitenberger P, et al. Lipoprotein apheresis for Lipoprotein(a)-associated cardiovascular disease: prospective 5 years of follow-up and Apolipoprotein(a) characterization. Arterioscler Thromb Vasc Biol. 2016;36(9):2019–27.
28. Marcovina SM, Albers JJ, Gabel B, Koschinsky ML, Gaur VP. Effect of the number of apolipoprotein(a) kringle 4 domains on immunochemical measurements of lipoprotein(a). Clin Chem. 1995;41(2):246–55.
29. Marcovina SM, Koschinsky ML. Lipoprotein(a) as a risk factor for coronary artery disease. Am J Cardiol. 1998;82(12a):57U-66U; discussion 86U.
30. McConnell JP, Guadagno PA, Dayspring TD, Hoefner DM, Thiselton DL, Warnick GR, et al. Lipoprotein(a) mass: a massively misunderstood metric. J Clin Lipidol. 2014;8(6):550–3.
31. Marcovina SM, Albers JJ, Scanu AM, Kennedy H, Giaculli F, Berg K, et al. Use of a reference material proposed by the international federation of clinical chemistry and laboratory medicine to evaluate analytical methods for the determination of plasma lipoprotein(a). Clin Chem. 2000;46(12):1956–67.
32. Matveyenko A, Matienzo N, Ginsberg H, Nandakumar R, Seid H, Ramakrishnan R, et al. Relationship of Apolipoprotein(a) isoform size with clearance and production of Lipoprotein(a) in a Diverse Cohort. J Lipid Res. 2023;64(3):100336.
33. Holleran S, Ramakrishnan R. cufunctions, a package to facilitate statistical analyses in R 2021 [http://biomath.net/cufunctions.html]. Available from: http://biomath.net/cufunctions.html.
34. Prevention. UCfDCa. National health and nutrition examination survey (NHANES). In: Services USDoHaH, editor.: National Center for Health Statistics (NCHS). March 28, 2022.
35. Sniderman AD, Thanassoulis G, Glavinovic T, Navar AM, Pencina M, Catapano A, et al. Apolipoprotein B particles and cardiovascular disease: a narrative review. JAMA cardiology. 2019;4(12):1287–95.
36. U.S. Department of Agriculture and U.S. Department of Health and Human Services. Dietary Guidelines for Americans, 2020–2025. 9th Edition. December 2020. DietaryGuidelines.gov.
37. Ebbeling CB, Knapp A, Johnson A, Wong JMW, Greco KF, Ma C, et al. Effects of a low-carbohydrate diet on insulin-resistant dyslipoproteinemia-a randomized controlled feeding trial. Am J Clin Nutr. 2022;115(1):154–62.
38. Late-breaking science abstracts and featured science abstracts from the American Heart association's scientific sessions 2022 and late-breaking abstracts in resuscitation science from the resuscitation science symposium 2022. Circulation. 2022;146(25):e569-e605.
39. Williams KA, Fughhi I, Fugar S, Mazur M, Gates S, Sawyer S, et al. Nutrition intervention for reduction of cardiovascular risk in African Americans using the 2019 American College of Cardiology/American Heart association primary prevention guidelines. Nutrients. 2021;13(10):3422.
40. Enkhmaa B, Petersen KS, Kris-Etherton PM, Berglund L. Diet and Lp(a): Does Dietary Change Modify Residual Cardiovascular Risk Conferred by Lp(a)? Nutrients. 2020;12(7):2024.
41. Feingold KR. The Effect of Diet on Cardiovascular Disease and Lipid and Lipoprotein Levels. In: Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, et al., editors. Endotext. South Dartmouth (MA)2000.
42. Roy R, Marakkar S, Vayalil MP, Shahanaz A, Anil AP, Km S, et al. Drug-food interactions in the era of molecular big data, machine intelligence, and personalized health. Recent Adv Food Nutr Agric. 2022;13(1):27–50.

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