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CURRENT DEVELOPMENTS IN NUTRITION

Circulating Concentrations of Essential Fatty Acids, Linoleic and α-Linolenic Acid, in US Adults in 2003–2004 and 2011–2012 and the Relation with Risk Factors for Cardiometabolic Disease: An NHANES Analysis

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ABSTRACT

Background: The increased use of high-oleic oils to replace *trans* fat has led to concern about declining intake of PUFA and the potential for essential fatty acid insufficiency or even deficiency.

Objectives: The aim of this study was to examine circulating concentrations of essential and poorly biosynthesized fatty acids, as biomarkers of dietary intake, in the NHANES data sets prior to (2003–2004 cycle) and following (2011–2012 cycle) legislation to reduce *trans* fat in the food supply and also to explore the associations between these fatty acids and markers of cardiometabolic health.

Methods: Fasting circulating concentrations of fatty acids from adults (aged ≥20 y) in the 2003–2004 and 2011–2012 NHANES cycles were used for analysis. Dietary data from one day of both the 2003–2004 and 2011–2012 cycles were used to examine differences in dietary fatty acid intake between these cycles. Regression analyses were used to assess relations between circulating concentrations of fatty acids and cardiometabolic health.

Results: Between the 2003–2004 and 2011–2012 NHANES cycles, LA dietary intake increased (1.38 g, $P = 0.002$); no difference in circulating concentrations was observed. ALA, measured by dietary intake (0.23 g, $P < 0.01$) and circulating concentrations (0.14%, $P < 0.001$), increased from 2003–2004 to 2011–2012. Circulating LA was inversely associated with BMI (in kg/m^2; regression coefficient per percentage point change in LA ± SE: –0.22 ± 0.04), waist circumference (–0.62 ± 0.09 cm), systolic blood pressure (–0.38 ± 0.09 mm Hg), triglycerides (–9.92 ± 0.63 mg/dL), glucose (–3.34 ± 0.13 mg/dL), insulin (–0.18 ± 0.05 μU/mL), and HOMA-IR (–0.29 ± 0.05).

Conclusions: In a nationally representative sample of US adults, no declines in circulating concentrations of essential fatty acids, LA and ALA, were observed between 2003–2004 and 2011–2012, a time when high-oleic oils were increasingly used in the food supply. Higher amounts of circulating LA were correlated with lower risk of cardiometabolic dysfunction, which underscores the importance of monitoring consumption in the United States. *Curr Dev Nutr* 2020;4:nzaa149.

Keywords: essential fatty acids, linoleic acid, α-linolenic acid, cardiovascular, cardiometabolic, *trans* fat, polyunsaturated fat, monounsaturated fat, omega-3 fatty acids

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Supplemental Tables 1–6 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/cdn/.

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Abbreviations used: AA, arachidonic acid; ALA, α-linolenic acid; CVD, cardiovascular disease; DPA, docosapentaenoic acid ; HbA1c, glycated hemoglobin; LA, linoleic acid; MESA, Multi-Ethnic Study of Atherosclerosis; PIR, poverty–income ratio; SFA, saturated fatty acid.

Introduction

In the United States, the use of plant oils (e.g., soybean, canola, and corn) in the production of processed foods contributes substantially to availability and intake of linoleic acid (LA) and α-linolenic acid (ALA). In the United States, LA and ALA comprise 6.8% and 0.7% of total energy intake, respectively, based on NHANES data from 2007–2014, which is approximately consistent with Adequate Intake recommendations (1). However, modifications to the US food supply to remove partially hydrogenated oils, containing *trans* fatty acids, are expected to reduce the

availability and intake of the essential PUFAs, LA and ALA (1). This is because partially hydrogenated oils are often replaced with oils that are lower in PUFAs and higher in MUFAs (2). Replacement of saturated fatty acids (SFAs) with unsaturated fatty acids, particularly PUFAs, is a cornerstone of cardiovascular disease (CVD) prevention (3). A decline in the availability of LA and ALA may result in a decrease in PUFA intake, which may make it more challenging to implement dietary recommendations to replace SFAs with PUFAs.

In 2003, the FDA mandated that if a product contained >0.5 g/serving of *trans* fatty acids, *trans* fat must be listed on the Nutrition Facts label; the compliance date was January 1, 2006 (4). This was followed by removal of the "generally recognized as safe" status from partially hydrogenated oils in June 2015, with a compliance date of June 2018 (5). One response to this was the development of high-oleic oils as a replacement for partially hydrogenated oils (6), leading to concerns about declining intake of PUFAs and the potential for essential fatty acid insufficiency or even deficiency (1). It is currently unclear how much high-oleic oil is being used in the food supply and whether use has reached a level that affects intake of essential fatty acids in US adults.

Accumulating evidence indicates that higher intake of LA and ALA is associated with lower risk of cardiometabolic diseases. In a pooled analysis of individual-level data from 20 prospective cohort studies, a higher proportion of circulating and adipose tissue LA, as a biomarker for LA intake, was associated with lower risk of type 2 diabetes (RR: 0.65; 95% CI: 0.60, 0.72) (7). In a similar analysis of 30 prospective cohort studies, circulating and adipose tissue LA were associated with lower risk of total CVD (HR: 0.93; 95% CI: 0.88, 0.99), cardiovascular mortality (HR: 0.78; 95% CI: 0.70, 0.85), and ischemic stroke (HR: 0.88; 95% CI: 0.79, 0.98) (8). Higher circulating and adipose tissue ALA concentrations have been associated with lower risk of CVD, particularly fatal coronary heart disease (9, 10). Evidence for the relation between ALA and type 2 diabetes is inconsistent (11). Thus, further investigation of the relation between essential fatty acids and risk of cardiometabolic diseases is warranted.

LA and ALA cannot be synthesized by humans, so circulating concentrations of these essential fatty acids are considered biomarkers of intake (12, 13) and are not subject to the complexities associated with measuring dietary intake. Conversely, circulating concentrations of saturated fats and MUFAs do not reflect intake because these fatty acids can be endogenously synthesized from carbohydrates (13–15). Few previous studies have examined the relation between objective markers of essential fatty acid intake and risk factors for cardiometabolic disease in a cohort representative of the US population. Furthermore, because changes in the availability of essential fatty acids in the food supply are expected, in response to reformulation efforts to remove *trans* fatty acids, examination of how circulating concentrations of essential fatty acids have changed prior to and in the time following legislation to lower *trans* fatty acids is needed. Therefore, we aimed to examine circulating concentrations of fatty acids as biomarkers of dietary intake with an emphasis on essential and poorly biosynthesized fatty acids in the 2003–2004 and 2011–2012 cycles of NHANES and describe the changes observed between the 2 time points. In addition, the association between circulating concentrations of essential and poorly biosynthesized fatty acids and markers of cardiometabolic health was evaluated.

Methods

Data from NHANES were used for these analyses. NHANES is a nationally representative cross-sectional survey conducted by the National Center for Health Statistics, CDC (16). The study protocol was approved by the National Center for Health Statistics research ethics review board. Written informed consent was obtained for all participants.

Assessment of circulating fatty acids

For these analyses, the 2003–2004 and 2011–2012 cycles were used because plasma/serum fatty acids were only available for these cycles. In 2003–2004, fasting plasma fatty acids were measured in participants aged ≥20 y, and in 2011–2012 serum fatty acids were measured in participants aged ≥1 y. Briefly, a modified version of the method described by Lagerstedt et al. (17) was used to measure total fatty acid concentrations in plasma/serum (18, 19). For the purposes of this article, we used data for the 15 fatty acids for which NHANES provided both dietary intake and plasma/serum concentrations. Circulating concentrations of essential (LA and ALA) and poorly biosynthesized fatty acids [eicosapentaenoic acid (EPA), DHA, and docosapentaenoic acid (DPA)] were of greatest interest because these are considered biomarkers of intake. Arachidonic acid (AA) was also examined because LA is a precursor to AA. The fatty acids were expressed as a percentage of total measured fatty acids.

Assessment of dietary intake

Dietary intake of fatty acids was determined as part of the What We Eat in America (the dietary intake interview component of the NHANES) survey (20, 21). For these analyses, the 24-h dietary recall obtained during the in-person health examination was used. The 24-h recall was collected using the USDA Automated Multiple-Pass Method (22). The Food and Nutrient Database for Dietary Studies 2011–2012 and the Food and Nutrient Database for Dietary Studies 2.0 were used to derive nutrient values from reported intakes in 2011–2012 and 2003–2004, respectively.

Assessment of cardiometabolic health

For assessment of cardiometabolic health, the following outcomes that are publicly available from NHANES were used for analysis: BMI (in kg/m^2), waist circumference, systolic blood pressure, diastolic blood pressure, fasting plasma glucose, plasma insulin, HOMA-IR, triglycerides, total cholesterol, LDL cholesterol, and HDL cholesterol. These assessments were done according to NHANES standard protocols (23). For reasons detailed further in NHANES documentation for each data set (24), not all individuals had values for all assessments.

Statistical analyses

Data analyzed were the fasting subsample from 2003–2004 and 2011–2012 for those aged ≥20 y ($n = 4489$) after exclusions for dietary records not deemed reliable ($n = 251$), pregnant or lactating women ($n = 147$), and subjects missing serum/plasma fatty acid data ($n = 317$). An analytical sample of 3809 was used.

Differences in demographics between the 2003–2004 and 2011–2012 samples were determined by *t* tests. Regression analyses were used to assess the relation between dietary intake of fatty acids and circulating plasma/serum concentrations. These analyses were conducted to

check that the relation between dietary intake of individual fatty acids and circulating concentrations aligns with published data on circulating biomarkers of fatty acid intake (i.e., essential and poorly biosynthesized PUFAs are biomarkers of intake, whereas circulating concentrations of MUFAs and SFAs do not correlate with intake) (13–15). Quartiles of plasma/serum essential and poorly biosynthesized fatty acid concentrations were established, and the relation with physiological measures was assessed by regression analyses after adjustment for potential confounders; for these analyses, data from 2003–2004 and 2011–2012 were pooled. These regression analyses employed 3 sets of covariates: model 1 adjusted for age, age^2, BMI, gender, ethnicity, total calorie intake, antihypertensive medication, antidiabetic medication, and antihyperlipidemic medication; model 2 adjusted for variables in model 1 + adjusted Healthy Eating Index (HEI)-2015 (adjusted by subtracting components 9 and 12 related to fatty acids from the total HEI score); and model 3 adjusted for model 2 + physical activity level (sedentary, moderate, or vigorous based on responses to the physical activity questionnaire), poverty–income ratio (PIR; <1.35, 1.35–1.85, and >1.85), and smoking status (yes/no). BMI was not included in models related to body weight, antihypertensive medication was not included in models evaluating blood pressure variables, antidiabetic medication was not included in models evaluating glucose- or insulin-related variables, and antihyperlipidemic medication was not included in models evaluating lipid variables.

Logistic regression was used to assess the OR of risk factors across quartiles of circulating concentrations of fatty acids, with the lowest quartile set as the reference group (OR = 1.0). The risk factors assessed were as follows: overweight or obesity: BMI ≥25; obesity: BMI ≥30; elevated waist circumference: >102 cm in men and >88 cm in women; elevated systolic blood pressure: ≥130 mm Hg or taking antihypertensive medications; elevated diastolic blood pressure: ≥80 mm Hg or taking antihypertensive medications; elevated total cholesterol: ≥200 mg/dL or taking antihyperlipidemic medications; elevated LDL cholesterol: ≥100 mg/dL or taking antihyperlipidemic medications; low HDL cholesterol: <40 mg/dL in men and <50 mg/dL in women or taking antihyperlipidemic medications; elevated triglycerides: ≥150 mg/dL or taking antihyperlipidemic medications; elevated fasting glucose, ≥100 mg/dL or taking insulin or other hypoglycemic agents; elevated fasting insulin: ≥15 μU/mL; and HOMA [plasma insulin (μU/mL) × plasma glucose (mg/dL)/405]: ≥4.0 (25). Metabolic syndrome was defined as the presence of ≥3 of the following criteria: elevated blood pressure, elevated waist circumference, elevated glucose, elevated triglycerides, and low HDL cholesterol as defined previously.

All statistical analyses used SAS 9.4 (SAS Institute) with survey parameters including primary sampling units, strata, and fasting subsample weights to provide nationally representative results (26). Statistical significance was set at $P < 0.01$.

Results

Cohort characteristics

Data were available for 1639 individuals in the 2003–2004 NHANES cycle and 2170 individuals in the 2011–2012 NHANES cycle (**Table 1**). No differences were observed between 2003–2004 and 2011–2012 with regard to sex, age, BMI, ethnicity, and use of antihypertensive medication. Compared with the 2003–2004 sample, a higher proportion of the 2011–2012 sample had a PIR <1.35, were taking lipid-lowering medication and hypoglycemic medication, reported moderate and vigorous physical activity levels, and never smoked.

Dietary intake of fatty acids and circulating concentrations in 2003–2004 and 2011–2012

Table 2 shows the correlation between dietary intake of essential and poorly biosynthesized fatty acids and circulating blood concentrations of these fatty acids. In 2003–2004 and 2011–2012, dietary intakes of ALA, EPA, DHA, and LA were weakly correlated with circulating concentrations of the respective fatty acids. In addition, weak correlations were observed between dietary intake of nonessential fatty acids myristic acid, stearic acid, and *cis*-vaccenic acid (**Supplemental Table 1**). Intake of AA was correlated with circulating concentrations in 2003–2004 only.

Between the 2003–2004 and 2011–2012 NHANES cycles, LA dietary intake increased (1.38 g, $P = 0.002$); no difference in circulating concentrations was observed. ALA, measured by dietary intake (0.23 g, $P < 0.01$) and circulating concentrations (0.14%, $P < 0.001$), increased from 2003–2004 to 2011–2012. Intake and circulating concentrations of γ-linolenic acid were higher in 2011–2012 compared with 2003–2004 (Supplemental Table 1). The quartile distribution of circulating LA and ALA and dietary intake was comparable in 2003–2004 and 2011–2012 (**Supplemental Table 2**). In contrast, intake and circulating concentrations of stearic acid, *cis*-vaccenic acid, and oleic acid were lower in 2011–2012 compared with 2003–2004 (Supplemental Table 1).

Because both ALA and LA compete for desaturation by Δ-6 desaturase in the biosynthesis of longer chain PUFAs, we examined the quartile ranking of ALA and LA (**Supplemental Tables 3** and **4**). For circulating LA and ALA, 51% of men and 48% of women were ranked in the same quartile. Furthermore, 37% of men and 40% of women were ranked within 1 quartile; in total, 88% of individuals were ranked in the same ALA/LA quartile or within 1 quartile.

Relation between circulating concentrations of essential and poorly biosynthesized fatty acids and risk factors for cardiometabolic disease

Higher concentrations of circulating LA were associated with lower BMI (regression coefficient per 1 percentage point increase: 0.22 kg/m^2, $P < 0.001$), waist circumference (0.62 cm, $P < 0.001$), systolic blood pressure (0.38 mm Hg, $P < 0.001$), triglycerides (9.92 mg/dL, $P < 0.001$), glucose (3.34 mg/dL, $P = 0.01$), insulin (0.18 μU/mL, $P < 0.001$), and HOMA-IR (0.07, $P < 0.001$) after multivariate adjustment when data from 2003–2004 and 2011–2012 were pooled (**Table 3**).

Higher circulating concentrations of ALA were associated with lower HDL cholesterol and higher triglycerides, glucose, insulin, and HOMA-IR; no other associations were detected for ALA. Circulating concentrations of EPA, DHA, and DPA were inversely associated with BMI, waist circumference, triglycerides, and glucose (**Supplemental Table 5**). Circulating concentrations of EPA and DHA were not related to systolic or diastolic blood pressure or insulin concentrations. Circulating EPA was positively associated with total cholesterol, LDL cholesterol, and HDL cholesterol; it was negatively associated with HOMA-IR. Circulating concentrations of DHA and DPA were not associated

TABLE 1 Characteristics of the sample

	Total population	2003–2004	2011–2012
n	3809	1639	2170
Sex, %			
Men	49	49	49
Women	51	51	51
Age, y	47 ± 0.5	47 ± 0.6	47 ± 0.8
BMI,[1] kg/m^2	28.6 ± 0.2	28.5 ± 0.2	28.8 ± 0.3
Ethnicity, %			
Non-Hispanic white	70	73	68
Non-Hispanic black	11	11	11
Mexican American	8	8	8
Other Hispanic	5	3	6
Other race	6	5	7
Poverty–income ratio,[2] %			
<1.35	24	20	27
1.35–1.85	10	10	10
>1.85	66	70	63
Antihypertensive medication, %			
Yes	28	26	31
No	72	74	69
Lipid-lowering medication, %			
Yes	17	14	19[3]
No	83	86	81
Hypoglycemic medication, %			
Yes	7	6	8
No	93	94	92
Physical activity, %			
Sedentary	27	34	21[3]
Moderate	37	35	40[3]
Vigorous	36	31	39[3]
Smoking, %			
Current	20	22	19
Former	28	30	26
Never	52	48	55[3]

[1]Total population, $n = 3762$; 2003–2004, $n = 1616$; 2011–2012, $n = 2146$.
[2]Total population, $n = 3554$; 2003–2004, $n = 1554$; 2011–2012, $n = 2000$.
[3]Compared with 2003–2004, $P < 0.01$.

with total cholesterol or LDL cholesterol. Higher DHA concentrations were associated with higher HDL cholesterol. Circulating DPA concentrations were positively associated with systolic blood pressure and inversely related to insulin and HOMA-IR.

Circulating concentrations of essential and poorly biosynthesized fatty acids and odds of risk factors for cardiometabolic disease

A higher circulating concentration of LA was associated with lower odds of overweight and obesity (linear trend OR: 0.93; 99% CI: 0.89, 0.96), obesity (OR: 0.94; 99% CI: 0.91, 0.97), enlarged waist circumference (OR: 0.92; 99% CI: 0.90, 0.95), metabolic syndrome (OR: 0.85; 99% CI: 0.81, 0.89), elevated total cholesterol (OR: 0.94; 99% CI: 0.91, 0.98), triglycerides (OR: 0.78; 99% CI: 0.76, 0.81), insulin (OR: 0.95; 99% CI: 0.92, 0.99) and HOMA-IR (OR: 0.95; 99% CI: 0.91, 0.99), and low HDL cholesterol (OR: 0.91; 99% CI: 0.88, 0.95) after adjustment for potential confounders (**Table 4**).

Higher blood concentrations of ALA were related to greater odds of metabolic syndrome (OR: 3.80; 99% CI: 1.99, 7.25), low HDL cholesterol (OR: 2.63; 99% CI: 1.60, 4.31), elevated triglycerides (OR: 6.94; 99% CI: 3.70, 13.03), glucose (OR: 2.01; 99% CI: 1.09, 3.72), insulin (OR: 5.32; 99% CI: 2.62, 10.79), and HOMA-IR (OR: 5.44; 99% CI: 2.81, 10.54) after multivariate adjustment.

Circulating concentrations of EPA were not associated with cardiometabolic disease risk factors (**Supplemental Table 6**). Higher circulating concentrations of DHA were related to lower odds of overweight and obesity (OR: 0.53; 99% CI: 0.41, 0.68), obesity (OR: 0.53; 99% CI: 0.39, 0.70), enlarged waist circumference (OR: 0.53; 99% CI: 0.38, 0.74), metabolic syndrome (OR: 0.68; 99% CI: 0.49, 0.95), and elevated triglycerides (OR: 0.74; 99% CI: 0.57, 0.96) after full adjustment for potential confounders. Higher blood concentrations of DPA were associated with lower odds of overweight and obesity (OR: 0.20; 99% CI: 0.06, 0.69), obesity (OR: 0.16; 99% CI: 0.04, 0.65), enlarged waist circumference (OR: 0.15; 99% CI: 0.04, 0.61), metabolic syndrome (OR: 0.16; 99% CI: 0.04, 0.66), elevated insulin concentrations (OR: 0.09; 99% CI: 0.02, 0.43), and HOMA-IR (OR: 0.10; 99% CI: 0.02, 0.46) after adjustment for potential confounders.

Discussion

In this representative sample of US adults in 2003–2004 and 2011–2012, circulating concentrations of essential (i.e., LA and ALA) and poorly

TABLE 2 Correlation between dietary intake of essential and poorly biosynthesized fatty acids and circulating blood levels in 2003–04 and 2011–12[1]

	2003–04				2011–12				Difference between the 2 time points			
	Dietary, (g)	Plasma, (%)	Regression coefficient	*P* value	Dietary, (g)	Serum, (%)	Regression coefficient	*P* value	Dietary, (g)	*P* value	Circulating levels (%)	*P* value
Linoleic acid (18:2n–6)	16.06 ± 0.32	31.26 ± 0.22	0.08 ± 0.01	<0.001	17.44 ± 0.25	31.73 ± 0.16	0.07 ± 0.01	<0.001	1.38 ± 0.41	0.002	0.47 ± 0.27	0.10
alpha-Linolenic acid (18:3n–3)	1.59 ± 0.03	0.60 ± 0.01	0.03 ± 0.01	<0.001	1.82 ± 0.03	0.74 ± 0.01	0.03 ± 0.01	<0.001	0.23 ± 0.04	<0.01	0.14 ± 0.01	<0.001
Eicosapentaenoic acid (20:5n–3)	0.04 ± 0.01	0.45 ± 0.01	0.97 ± 0.21	<0.001	0.03 ± 0.003	0.58 ± 0.02	1.32 ± 0.28	<0.001	–0.01 ± 0.01	0.04	0.13 ± 0.03	<0.001
Docosapentaenoic acid (22:5n–3)	0.02 ± 0.002	0.39 ± 0.004	0.19 ± 0.11	0.10	0.02 ± 0.001	0.44 ± 0.004	0.18 ± 0.12	0.13	0.004 ± 0.002	0.17	0.05 ± 0.01	<0.001
Docosahexaenoic acid (22:6n–3)	0.08 ± 0.01	1.22 ± 0.04	0.90 ± 0.20	<0.001	0.06 ± 0.004	1.33 ± 0.05	1.04 ± 0.15	<0.001	–0.02 ± 0.01	0.03	0.11 ± 0.06	0.06

[1]Values are means ± SEs unless otherwise stated.

biosynthesized fatty acids (i.e., EPA, DPA, and DHA) were correlated with dietary intake. In addition, relative to the 2003–2004 NHANES cycle, no difference in circulating LA was observed in 2011–2012, suggesting no change in intake. Both circulating ALA and dietary intake were higher in 2011–2012 versus 2003–2004. Furthermore, circulating LA was inversely associated with BMI, waist circumference, systolic blood pressure, triglycerides, glucose, insulin, and HOMA-IR when data from both time points were pooled. In alignment, odds of overweight and obesity, enlarged waist circumference, metabolic syndrome, and markers of dysglycemia were lower with increasing concentrations of circulating LA. Higher circulating concentrations of ALA were unfavorably correlated with a number of cardiometabolic risk factors. However, higher circulating concentrations of EPA, DPA, and DHA were favorably associated with many of the cardiometabolic risk factors examined. Therefore, the ALA findings should be interpreted with caution because they may reflect physiological differences, particularly in the bioconversion to longer chain omega-3 (n–3) fatty acids. These analyses suggest that intake of essential fatty acids has not declined with reformulation efforts to remove *trans* fatty acids during the time period studied. Furthermore, higher circulating LA is correlated with lower risk of cardiometabolic dysfunction.

Historically, the cardiovascular effects of LA have been controversial. This stemmed from hypotheses about the pro-inflammatory potential of AA, a metabolic product of LA. However, there is now widespread agreement that LA is not adversely associated with CVD, and replacement of saturated fat with PUFA confers CVD benefit (3, 27). Our findings that higher circulating LA concentrations are associated with less adiposity and lower triglycerides, glucose, insulin, and HOMA-IR are consistent with previous evidence. In clinical trials (28, 29) and epidemiologic studies (30, 31), higher intake of LA has been favorably related to adiposity and glycemic control. In the Multi-Ethnic Study of Atherosclerosis (MESA) cohort, an inverse relation was observed between phospholipid LA concentrations and BMI such that those with the highest phospholipid LA concentrations had a 1.10 kg/m^2 (95% CI: –1.50, –0.71) lower BMI compared with those with the lowest LA concentrations in a cross-sectional analysis at baseline; no relation was observed between 10-y BMI change and baseline LA concentrations (31). Furthermore, in a cross-sectional analysis of US adults, erythrocyte LA concentrations were inversely associated with trunk adipose measured by DXA (30). In addition to favorable associations with adiposity, higher circulating concentrations of LA have been associated with lower risk of type 2 diabetes in prospective analyses (8). Similarly, in randomized controlled trials, isocaloric replacement of carbohydrate or saturated fat with PUFAs (predominately LA) lowered glycated hemoglobin (HbA1c) and improved insulin sensitivity (28). In randomized controlled trials, diets enriched in n–6 PUFA have also been shown to reduce liver fat (29) and abdominal subcutaneous fat (32) compared with diets higher in saturated fat.

In our analyses, we observed a positive relation between circulating LA concentrations and LDL cholesterol, which does not align with the well-established lipid lowering observed when saturated fat is replaced with PUFA (33) or the lipid-lowering effects of LA-rich food sources. In a double-blind, randomized, crossover study, Maki et al. (34) showed that consumption of 4 tablespoons of corn oil (54 g/d; ∼30 g of LA) lowered LDL cholesterol (–7.4%), non-HDL cholesterol (–7.7%), and total cholesterol (–6.4%) to a greater extent than

TABLE 3 Association between circulating concentrations of essential fatty acids and risk factors for cardiometabolic disease: NHANES 2003–2004 and 2011–2012 combined[1]

	Circulating fatty acid quartiles, % (99% CI)				Linear trend	
	1	2	3	4	$\beta \pm$ SE	*P* value
LA	25.35 (25.05, 25.65)	30.29 (30.17, 30.41)	33.20 (33.12, 33.28)	37.15 (36.92, 37.37)		
BMI,[2] kg/m^2	29.7 (28.9, 30.5)	29.4 (28.6, 30.1)	28.1 (27.4, 28.8)	27.0 (26.0, 27.9)	–0.22 ± 0.04	<0.001
Waist circumference,[2] cm	101.8 (99.9, 103.7)	100.2 (98.4, 102.1)	96.9 (95.4, 98.5)	94.2 (91.9, 96.4)	–0.62 ± 0.09	<0.001
Systolic blood pressure,[3] mm Hg	124 (122, 126)	122 (120, 124)	121 (119, 123)	120 (118, 122)	–0.38 ± 0.09	<0.001
Diastolic blood pressure,[3] mm Hg	72 (70, 73)	71 (70, 73)	71 (70, 73)	70 (69, 72)	–0.11 ± 0.06	0.08
Total cholesterol,[4] mg/dL	201 (193, 208)	198 (194, 202)	195 (190, 200)	195 (189, 200)	–0.61 ± 0.29	0.04
LDL cholesterol,[4] mg/dL	109 (103, 115)	119 (116, 123)	118 (114, 121)	120 (116,125)	1.01 ± 0.25	<0.001
HDL cholesterol,[4] mg/dL	51 (49, 54)	53 (51, 55)	54 (53, 56)	55 (54, 57)	0.33 ± 0.08	<0.001
Triglycerides,[4] mg/dL	207 (188, 225)	129 (121,136)	115 (108, 122)	95 (89, 100)	–9.92 ± 0.63	<0.001
Glucose,[5] mg/dL	105 (102, 109)	101 (99, 104)	100 (98, 102)	102 (100, 104)	–0.34 ± 0.13	0.01
Insulin,[5] μU/mL	12.6 (11.3, 13.9)	12.5 (10.8, 14.2)	11.0 (10.1, 11.9)	11.0 (10.0, 12.1)	–0.18 ± 0.05	<0.001
HOMA-IR[5]	3.5 (3.0, 4.0)	3.3 (2.7, 3.7)	2.9 (2.4, 3.3)	2.9 (2.5, 3.3)	–0.07 ± 0.02	<0.001
ALA	0.42 (0.40, 0.43)	0.56 (0.56, 0.56)	0.70 (0.69, 0.71)	0.99 (0.97, 1.01)		
BMI,[2] kg/m^2	28.3 (27.6, 29.1)	28.6 (27.9, 29,2)	29.0 (28.1, 29.8)	28.3 (27.7, 29.0)	0.16 ± 0.53	0.76
Waist circumference,[2] cm	97.3 (95.4, 99.3)	98.2 (96.5, 99.9)	99.3 (97.4, 101.2)	98.2 (96.5, 99.9)	1.20 ± 1.36	0.38
Systolic blood pressure,[3] mm Hg	123 (120, 126)	122 (120, 124)	121 (120, 123)	122 (119, 124)	–1.69 ± 1.97	0.40
Diastolic blood pressure,[3] mm Hg	72 (70, 74)	72 (70,73)	71 (69, 72)	71 (69, 72)	–1.35 ± 1.25	0.29
Total cholesterol,[4] mg/dL	197 (194, 200)	194 (190, 199)	197 (192, 202)	200 (195, 205)	4.63 ± 3.34	0.18
LDL cholesterol,[4] mg/dL	117 (114, 121)	115 (111, 119)	117 (112, 122)	118 (113, 122)	–0.24 ± 3.27	0.94
HDL cholesterol,[4] mg/dL	57 (55, 59)	55 (53, 57)	53 (52, 55)	49 (48, 50)	–12.51 ± 1.23	<0.001
Triglycerides,[4] mg/dL	113 (104, 122)	122 (114, 129)	135 (124, 145)	174 (156, 192)	112 ± 15.61	<0.001
Glucose,[5] mg/dL	100 (97, 103)	101 (99, 104)	104 (102, 106)	104 (101, 106)	6.43 ± 2.16	0.006
Insulin,[5] μU/mL	10.2 (9.5, 11.0)	11.3 (9.9, 12.6)	11.5 (10.7, 12.4)	14.1 (12.3, 15.8)	6.25 ± 1.16	<0.001
HOMA-IR[5]	2.7 (2.2, 3.1)	3.0 (2.5, 3.5)	3.1 (2.7, 3.5)	3.8 (3.2, 4.3)	1.80 ± 0.32	<0.001

[1]Values are least square means (95% CI), unless otherwise stated, adjusted for age, age^2, BMI, gender, ethnicity, calorie intake, antihypertensive medication, antidiabetic medication, antihyperlipidemic medication, adjusted HEI-2015 (adjusted subtracting components 9 and 12 related to fatty acids from the total HEI score), physical activity level, PIR, and smoking status. ALA, α-linolenic acid; HEI, Healthy Eating Index; LA, linoleic acid; PIR, poverty–income ratio.
[2]Not adjusted for BMI.
[3]Not adjusted for antihypertensive medication.
[4]Not adjusted for antihyperlipidemic medication.
[5]Not adjusted for antidiabetic medication.

TABLE 4 Circulating concentrations of essential fatty acids and odds of risk factors for cardiometabolic disease: NHANES 2003–2004 and 2011–2012 combined[1]

	Plasma fatty acid quartiles					
	1	2	3	4	Quartile trend	Linear trend
LA						
Overweight or obesity						
Model 1[2]	Ref	0.81 (0.56, 1.16)	0.58 (0.42, 0.79)	0.46 (0.29, 0.72)	0.76 (0.66, 0.88)	0.93 (0.90, 0.97)
Model 2	Ref	0.81 (0.56, 1.17)	0.58 (0.43, 0.80)	0.46 (0.29, 0.72)	0.77 (0.67, 0.88)	0.93 (0.90, 0.97)
Model 3	Ref	0.82 (0.57, 1.19)	0.59 (0.42, 0.84)	0.44 (0.27, 0.69)	0.75 (0.65, 0.87)	0.93 (0.89, 0.96)
Obesity						
Model 1[2]	Ref	0.87 (0.62, 1.21)	0.67 (0.46, 0.97)	0.46 (0.31, 0.69)	0.78 (0.69, 0.87)	0.94 (0.92, 0.97)
Model 2	Ref	0.86 (0.61, 1.21)	0.67 (0.46, 0.98)	0.47 (0.31, 0.70)	0.78 (0.69, 0.88)	0.95 (0.92, 0.97)
Model 3	Ref	0.88 (0.59, 1.30)	0.67 (0.44, 1.02)	0.46 (0.29, 0.73)	0.77 (0.67, 0.89)	0.94 (0.91, 0.97)
Enlarged waist circumference						
Model 1[2]	Ref	0.68 (0.50, 0.94)	0.53 (0.39, 0.72)	0.40 (0.27, 0.59)	0.74 (0.65, 0.84)	0.93 (0.90, 0.96)
Model 2	Ref	0.68 (0.49, 0.94)	0.53 (0.39, 0.72)	0.40 (0.27, 0.60)	0.74 (0.65, 0.84)	0.93 (0.90, 0.96)
Model 3	Ref	0.68 (0.49, 0.95)	0.54 (0.39, 0.75)	0.38 (0.25, 0.59)	0.73 (0.64, 0.84)	0.92 (0.90, 0.95)
Metabolic syndrome						
Model 1[2,3,4,5]	Ref	0.44 (0.32, 0.59)	0.27 (0.18, 0.39)	0.16 (0.10, 0.26)	0.55 (0.47, 0.65)	0.85 (0.81, 0.89)
Model 2	Ref	0.43 (0.32, 0.59)	0.27 (0.18, 0.40)	0.16 (0.10, 0.26)	0.55 (0.47, 0.65)	0.85 (0.82, 0.89)
Model 3	Ref	0.46 (0.33, 0.64)	0.27 (0.18, 0.42)	0.17 (0.10, 0.27)	0.55 (0.46, 0.66)	0.85 (0.81, 0.89)
Elevated systolic blood pressure						
Model 1[3]	Ref	0.77 (0.46, 1.29)	0.67 (0.42, 1.08)	0.69 (0.46, 1.05)	0.88 (0.78, 1.00)	0.96 (0.93, 1.00)
Model 2	Ref	0.76 (0.45, 1.29)	0.68 (0.42, 1.10)	0.70 (0.46, 1.08)	0.89 (0.78, 1.01)	0.97 (0.93, 1.00)
Model 3	Ref	0.74 (0.43, 1.26)	0.66 (0.40, 1.08)	0.70 (0.44, 1.09)	0.89 (0.77, 1.02)	0.97 (0.93, 1.00)
Elevated diastolic blood pressure						
Model 1[3]	Ref	0.84 (0.55, 1.28)	0.65 (0.40, 1.04)	0.66 (0.43, 1.03)	0.86 (0.75, 0.99)	0.96 (0.93, 0.99)
Model 2	Ref	0.83 (0.54, 1.27)	0.65 (0.40, 1.05)	0.67 (0.43, 1.04)	0.86 (0.75, 0.99)	0.96 (0.93, 1.00)
Model 3	Ref	0.84 (0.55, 1.29)	0.67 (0.41, 1.10)	0.66 (0.41, 1.08)	0.86 (0.74, 1.00)	0.96 (0.93, 1.00)
Elevated total cholesterol						
Model 1[4]	Ref	0.75 (0.51, 1.10)	0.59 (0.38, 0.91)	0.51 (0.34, 0.76)	0.80 (0.70, 0.92)	0.95 (0.91, 0.98)
Model 2	Ref	0.75 (0.52, 1.10)	0.59 (0.38, 0.90)	0.51 (0.34, 0.75)	0.80 (0.70, 0.91)	0.95 (0.91, 0.98)
Model 3	Ref	0.77 (0.51, 1.14)	0.59 (0.37, 0.93)	0.50 (0.33, 0.75)	0.79 (0.69, 0.90)	0.94 (0.91, 0.98)
Elevated LDL cholesterol						
Model 1[4]	Ref	1.36 (0.86, 2.16)	1.54 (0.92, 2.56)	1.43 (0.86, 2.38)	1.12 (0.94, 1.34)	1.03 (0.98, 1.08)
Model 2	Ref	1.36 (0.86, 2.16)	1.54 (0.93, 2.56)	1.43 (0.86, 2.37)	1.12 (0.94, 1.34)	1.03 (0.98, 1.08)
Model 3	Ref	1.38 (0.86, 2.21)	1.60 (0.96, 2.66)	1.44 (0.88, 2.35)	1.12 (0.95, 1.34)	1.03 (0.99, 1.08)
Low HDL cholesterol						
Model 1[4]	Ref	0.55 (0.39, 0.78)	0.43 (0.28, 0.65)	0.40 (0.26, 0.61)	0.73 (0.64, 0.84)	0.91 (0.88, 0.94)
Model 2	Ref	0.54 (0.38, 0.77)	0.43 (0.28, 0.65)	0.40 (0.26, 0.61)	0.74 (0.64, 0.85)	0.91 (0.88, 0.94)
Model 3	Ref	0.57 (0.38, 0.84)	0.43 (0.28, 0.67)	0.41 (0.25, 0.65)	0.74 (0.63, 0.86)	0.91 (0.88, 0.95)
Elevated triglycerides						
Model 1[4]	Ref	0.25 (0.17, 0.37)	0.16 (0.11, 0.23)	0.07 (0.05, 0.10)	0.43 (0.39, 0.48)	0.78 (0.76, 0.81)
Model 2	Ref	0.25 (0.17, 0.37)	0.16 (0.11, 0.23)	0.07 (0.05, 0.10)	0.43 (0.39, 0.48)	0.78 (0.76, 0.81)
Model 3	Ref	0.24 (0.16, 0.38)	0.16 (0.11, 0.23)	0.07 (0.05, 0.11)	0.43 (0.38, 0.49)	0.78 (0.76, 0.81)
Elevated glucose						
Model 1[5]	Ref	0.87 (0.58, 1.31)	0.81 (0.56, 1.16)	0.79 (0.54, 1.16)	0.92 (0.82, 1.04)	0.98 (0.95, 1.00)
Model 2	Ref	0.87 (0.58, 1.31)	0.81 (0.56, 1.16)	0.79 (0.54, 1.16)	0.92 (0.82, 1.04)	0.98 (0.95, 1.00)
Model 3	Ref	0.92 (0.62, 1.38)	0.83 (0.57, 1.22)	0.82 (0.57, 1.20)	0.93 (0.84, 1.04)	0.98 (0.95, 1.01)
Elevated insulin						
Model 1[5]	Ref	0.76 (0.50, 1.14)	0.56 (0.43, 0.72)	0.63 (0.38, 1.02)	0.83 (0.73, 0.96)	0.95 (0.92, 0.99)
Model 2	Ref	0.75 (0.50, 1.14)	0.56 (0.43, 0.72)	0.63 (0.38, 1.02)	0.83 (0.73, 0.96)	0.95 (0.91, 0.99)
Model 3	Ref	0.80 (0.54, 1.19)	0.55 (0.43, 0.72)	0.68 (0.41, 1.11)	0.85 (0.74, 0.97)	0.95 (0.92, 0.99)
Elevated HOMA-IR						
Model 1[5]	Ref	0.71 (0.45, 1.13)	0.55 (0.36, 0.82)	0.61 (0.33, 1.10)	0.83 (0.70, 0.98)	0.95 (0.90, 0.99)
Model 2	Ref	0.71 (0.45, 1.13)	0.55 (0.36, 0.83)	0.61 (0.33, 1.10)	0.83 (0.70, 0.98)	0.95 (0.90, 0.99)
Model 3	Ref	0.77 (0.49, 1.20)	0.57 (0.39, 0.85)	0.67 (0.36, 1.22)	0.85 (0.72, 1.01)	0.95 (0.91, 0.99)
ALA						
Overweight or obesity						
Model 1[2]	Ref	1.21 (0.86, 1.69)	1.45 (1.02, 2.05)	1.27 (0.91, 1.79)	1.10 (0.98, 1.22)	1.57 (0.93, 2.64)
Model 2	Ref	1.20 (0.86, 1.68)	1.47 (1.03, 2.08)	1.31 (0.94, 1.81)	1.11 (1.00, 1.23)	1.67 (1.01, 2.77)
Model 3	Ref	1.11 (0.79, 1.56)	1.35 (0.96, 1.90)	1.26 (0.91, 1.73)	1.09 (0.99, 1.21)	1.56 (0.95, 2.55)
Obesity						
Model 1[2]	Ref	1.18 (0.84, 1.66)	1.37 (1.01, 1.87)	0.88 (0.64, 1.23)	0.98 (0.89, 1.09)	0.84 (0.53, 1.32)

(*Continued*)

TABLE 4 (*Continued*)

	Plasma fatty acid quartiles					
	1	2	3	4	Quartile trend	Linear trend
Model 2	Ref	1.17 (0.83, 1.64)	1.39 (1.01, 1.90)	0.91 (0.66, 1.24)	0.99 (0.90, 1.09)	0.89 (0.57, 1.37)
Model 3	Ref	1.15 (0.82, 1.61)	1.42 (1.01, 2.00)	0.90 (0.63, 1.29)	0.99 (0.88, 1.11)	0.89 (0.55, 1.46)
Enlarged waist circumference						
Model 1[2]	Ref	1.18 (0.84, 1.65)	1.27 (0.87, 1.86)	1.13 (0.81, 1.57)	1.04 (0.93, 1.17)	1.12 (0.70, 1.80)
Model 2	Ref	1.17 (0.83, 1.65)	1.29 (0.87, 1.90)	1.16 (0.83, 1.62)	1.06 (0.94, 1.19)	1.20 (0.75, 1.90)
Model 3	Ref	1.11 (0.77, 1.60)	1.22 (0.82, 1.83)	1.11 (0.78, 1.58)	1.04 (0.92, 1.18)	1.11 (0.67, 1.84)
Metabolic syndrome						
Model 1[2,3,4,5]	Ref	1.00 (0.64, 1.56)	1.21 (0.79, 1.84)	1.83 (1.18, 2.84)	1.22 (1.05, 1.42)	3.00 (1.58, 5.67)
Model 2	Ref	1.00 (0.64, 1.57)	1.23 (0.80, 1.90)	1.91 (1.23, 2.94)	1.24 (1.07, 1.44)	3.29 (1.74, 6.21)
Model 3	Ref	1.00 (0.63, 1.59)	1.29 (0.82, 2.04)	2.00 (1.30, 3.08)	1.27 (1.09, 1.47)	3.80 (1.99, 7.25)
Elevated systolic blood pressure						
Model 1[3]	Ref	0.71 (0.45, 1.11)	0.89 (0.61, 1.30)	1.13 (0.73, 1.77)	1.07 (0.92, 1.23)	1.40 (0.77, 2.55)
Model 2	Ref	0.70 (0.45, 1.10)	0.91 (0.61, 1.37)	1.17 (0.76, 1.82)	1.08 (0.93, 1.25)	1.51 (0.82, 2.80)
Model 3	Ref	0.66 (0.40, 1.10)	0.86 (0.57, 1.28)	1.08 (0.68, 1.72)	1.05 (0.90, 1.23)	1.41 (0.70, 2.84)
Elevated diastolic blood pressure						
Model 1[3]	Ref	0.89 (0.54, 1.46)	0.93 (0.65, 1.33)	1.24 (0.80, 1.91)	1.07 (0.94, 1.23)	1.32 (0.72, 2.44)
Model 2	Ref	0.89 (0.54, 1.45)	0.95 (0.66, 1.36)	1.27 (0.82, 1.96)	1.08 (0.94, 1.24)	1.39 (0.75, 2.59)
Model 3	Ref	0.84 (0.51, 1.37)	0.94 (0.66, 1.34)	1.26 (0.80, 1.97)	1.09 (0.94, 1.25)	1.43 (0.72, 2.83)
Elevated total cholesterol						
Model 1[4]	Ref	1.00 (0.74, 1.36)	1.16 (0.75, 1.80)	1.09 (0.78, 1.53)	1.04 (0.93, 1.17)	1.10 (0.70, 1.73)
Model 2	Ref	1.01 (0.74, 1.37)	1.16 (0.75, 1.80)	1.08 (0.78, 1.52)	1.04 (0.93, 1.16)	1.07 (0.67, 1.72)
Model 3	Ref	1.07 (0.78, 1.48)	1.20 (0.76, 1.91)	1.17 (0.83, 1.66)	1.06 (0.94, 1.19)	1.16 (0.70, 1.91)
Elevated LDL cholesterol						
Model 1[4]	Ref	0.91 (0.70, 1.19)	1.01 (0.66, 1.55)	0.92 (0.59, 1.44)	0.99 (0.85, 1.14)	0.84 (0.42, 1.67)
Model 2	Ref	0.91 (0.70, 1.19)	1.01 (0.66, 1.54)	0.92 (0.59, 1.43)	0.99 (0.85, 1.14)	0.84 (0.43, 1.65)
Model 3	Ref	0.93 (0.72, 1.21)	1.01 (0.66, 1.53)	0.92 (0.60, 1.43)	0.98 (0.85, 1.14)	0.78 (0.38, 1.59)
Low HDL cholesterol						
Model 1[4]	Ref	1.15 (0.81, 1.62)	0.96 (0.66, 1.38)	1.63 (1.19, 2.24)	1.14 (1.02, 1.28)	2.35 (1.45, 3.82)
Model 2	Ref	1.14 (0.82, 1.60)	0.97 (0.68, 1.38)	1.67 (1.23, 2.27)	1.15 (1.03, 1.28)	2.50 (1.56, 4.00)
Model 3	Ref	1.27 (0.87, 1.86)	1.07 (0.73, 1.55)	1.77 (1.28, 2.43)	1.17 (1.05, 1.31)	2.63 (1.60, 4.31)
Elevated triglycerides						
Model 1[4]	Ref	1.16 (0.83, 1.60)	1.26 (0.82, 1.93)	2.59 (1.69, 3.96)	1.35 (1.17, 1.57)	5.61 (2.96, 10.65)
Model 2	Ref	1.15 (0.83, 1.60)	1.27 (0.83, 1.94)	2.65 (1.74, 4.02)	1.36 (1.18, 1.58)	5.94 (3.17, 11.15)
Model 3	Ref	1.17 (0.79, 1.72)	1.38 (0.85, 2.23)	2.83 (1.83, 4.40)	1.40 (1.21, 1.63)	6.94 (3.70, 13.03)
Elevated glucose						
Model 1[5]	Ref	1.04 (0.66, 1.64)	1.39 (0.90, 2.15)	1.39 (0.88, 2.22)	1.14 (0.99, 1.31)	1.80 (1.04, 3.13)
Model 2	Ref	1.04 (0.66, 1.64)	1.40 (0.90, 2.16)	1.40 (0.87, 2.24)	1.14 (0.99, 1.31)	1.81 (1.02, 3.20)
Model 3	Ref	1.09 (0.66, 1.78)	1.52 (0.94, 2.43)	1.45 (0.88, 2.38)	1.15 (0.99, 1.34)	2.01 (1.09, 3.72)
Elevated insulin						
Model 1[5]	Ref	1.36 (0.84, 2.18)	1.87 (1.31, 2.67)	2.77 (1.74, 4.39)	1.40 (1.21, 1.63)	4.69 (2.55, 8.63)
Model 2	Ref	1.35 (0.85, 2.16)	1.90 (1.33, 2.71)	2.82 (1.77, 4.51)	1.42 (1.21, 1.65)	4.94 (2.57, 9.48)
Model 3	Ref	1.34 (0.82, 2.17)	1.88 (1.26, 2.81)	2.90 (1.81, 4.67)	1.43 (1.21, 1.69)	5.32 (2.62, 10.79)
Elevated HOMA-IR						
Model 1[5]	Ref	1.45 (0.87, 2.43)	2.00 (1.38, 2.91)	2.94 (1.87, 4.62)	1.43 (1.24, 1.64)	4.54 (2.58, 7.98)
Model 2	Ref	1.45 (0.87, 2.40)	2.03 (1.40, 2.94)	2.99 (1.90, 4.70)	1.44 (1.25, 1.66)	4.76 (2.62, 8.64)
Model 3	Ref	1.45 (0.87, 2.43)	2.04 (1.36, 3.05)	3.19 (1.99, 5.11)	1.47 (1.26, 1.71)	5.44 (2.81, 10.54)

[1]Values are OR (99% CI). Model 1 adjusted for age, age[2], BMI, gender, ethnicity, calorie intake, antihypertensive medication, antidiabetic medication, and antihyperlipidemic medication. Model 2 adjusted for variables in model 1 + adjusted HEI-2015 (adjusted by subtracting components 9 and 12 related to fatty acids from the total HEI score). Model 3 adjusted for model 2 + physical activity level, PIR, and smoking status. ALA, α-linolenic acid; HEI, Healthy Eating Index; LA, linoleic acid; PIR, poverty–income ratio.
[2]Model not adjusted for BMI.
[3]Model not adjusted for antihypertensive medication.
[4]Model not adjusted for antihyperlipidemic medication.
[5]Model not for antidiabetic medication.

4 tablespoons of extra virgin olive oil rich in MUFA after 3 wk in adults with elevated LDL cholesterol. Further analyses showed that corn oil reduced atherogenic lipoprotein cholesterol and particle concentrations to a greater extent than extra virgin olive oil (35). In a similar trial by the same authors, consumption of 4 tablespoons/d of corn oil improved lipids/lipoproteins relative to 4 tablespoons/d of coconut oil (36). Soybean and canola oil also contain appreciable amounts of LA, and in clinical trials lipid lowering has been observed with these oils (37).

These oils are not only a source of LA but also contain other fatty acids and phytosterols. The consistent evidence showing lipid lowering with higher intake of these LA-rich oils suggests no adverse effects of LA on lipids/lipoproteins (38). Thus, our finding that higher circulating concentrations of LA are associated with higher LDL-cholesterol is not likely to be causative. LDL is a major carrier of LA, and ∼35% of the total fatty acid composition of LDL is LA (39); therefore, our finding may reflect collinearity.

Our analyses show a positive association between circulating ALA concentrations and triglycerides, glucose, insulin, and HOMA-IR, and a negative association with HDL cholesterol. Similar to our results, in MESA, higher phospholipid ALA was positively associated with triglycerides in a cross-sectional analysis (40). This does not align with evidence suggesting higher ALA consumption is associated with lower risk of type 2 diabetes (9) and CVD (9, 10, 41), particularly fatal CHD (9, 10). In addition, a meta-analysis of 8 randomized controlled trials showed no effect of ALA on HbA1c, fasting glucose, or insulin (42). Thus, it is likely that our findings reflect differences in metabolism of ALA at high and low circulating concentrations. ALA and LA both undergo desaturation by Δ-6 desaturase in the biosynthesis of longer chain PUFAs, and higher concentrations of LA decrease the conversion of ALA to EPA and DHA (43). In our analyses, ∼50% of individuals were ranked in the same quartile for circulating ALA and LA concentrations, and a high proportion of individuals with the highest concentrations of circulating ALA also had the highest concentrations of circulating LA. Therefore, higher ALA concentrations may reflect lower bioconversion, not higher ALA intake. Bioconversion of ALA to EPA/DHA is typically low (<5%); the majority of ALA is β-oxidized (43). It has been suggested that ALA may be more strongly associated with cardioprotection when the diet is completely devoid of EPA and DHA, although this requires further investigation (3). Thus, because ALA has a very short half-life (1 h) in plasma (44) and is utilized in many metabolic pathways, the biological relevance of our findings is unclear, but the relations observed are unlikely to be causal.

We observed that higher circulating concentrations of EPA and DHA were inversely associated with BMI, waist circumference, triglycerides, and glucose. It is well established that EPA and DHA supplementation reduces triglycerides (45), which is consistent with our observation that higher circulating concentrations of EPA and DHA were associated with lower triglyceride concentrations. Glucose-lowering effects of EPA and DHA have not been observed consistently in human trials; the most recent meta-analysis of randomized controlled trials showed no effect of EPA and DHA supplementation on HbA1c, HOMA-IR, fasting insulin, or fasting glucose (46). Similarly, previous studies have not shown associations between EPA and DHA and measures of adiposity. Consequently, these findings should be interpreted cautiously and require further investigation using prospective analyses.

Modeling analyses have suggested that increased use of high-oleic oils in the food supply will result in an increase in the availability and intake of MUFAs at the expense of PUFAs, especially LA (1, 47). However, it is unclear how widespread the use of high-oleic oil is in the food supply and the concomitant reduction in conventional oil use; examination of this is needed. In our analyses, circulating concentrations of LA did not change between 2003–2004 and 2011–2012, representing time points prior to widespread reformulation to remove *trans* fatty acids and 5–6 y following the mandate to list *trans* fatty acids on the Nutrition Facts label, respectively. This suggests high-oleic oil use did not reach a concentration that impacted essential fatty acid intake of the US adult population between 2003–2004 and 2011–2012. Our analyses showed a modest increase in dietary intake of LA between the 2 time points, but no change in circulating concentrations of LA, which is considered a more objective biomarker of intake. Our findings should be interpreted cautiously because the compliance date for removal of partially hydrogenated oils from food products was June 2018, so reformulation has likely occurred since 2011–2012. However, the FDA estimates that between 2003 and 2010, intake of *trans* fatty acids was reduced from 4.6 g/person/d to 1.3 g/person/d (72% decrease), with a further reduction to 1.0 g/person/d in 2012 (48). Further investigation of changes in circulating concentrations of LA since 2012 is warranted; these data are not currently available in NHANES.

To the authors' knowledge, this is the first article to describe circulating essential and poorly biosynthesized fatty acid concentrations in a representative sample of US adults (i.e., NHANES) and relate these to risk factors for cardiometabolic disease. However, these results should be interpreted in the context of several limitations. First, these analyses are cross-sectional, and causation cannot be determined. In addition, plasma/serum samples were used to measure fatty acid concentrations, which only reflect intake within the past few weeks. Erythrocyte or adipose tissue fatty acids are superior for characterizing usual intake because they are less sensitive to recent intake (13). In addition, although circulating concentrations of essential or poorly biosynthesized fatty acids are biomarkers of dietary intake, concentrations are affected by various processes, including intestinal absorption, metabolism and storage, and exchange among compartments, and therefore results do not reflect only dietary intake. Outcomes assessed were limited to those publicly available in the NHANES data sets used, which limited our ability to examine how circulating concentrations of essential fatty acids associated with site-specific related adiposity outcomes (e.g., visceral and subcutaneous adipose tissue). Finally, dietary intake was assessed using a single 24-h recall, which may not approximate habitual intake, and the nutrient databases used to derive fatty acid intake may not accurately reflect actual fatty acid intake because of temporal changes in food product composition.

In conclusion, in a representative sample of US adults, no decline in circulating concentrations of essential fatty acids, LA and ALA, was observed between 2003–2004 and 2011–2012, suggesting intake has not been affected by efforts to reduce *trans* fat in the food supply. Higher circulating concentrations of LA were associated with lower risk of metabolic dysfunction, suggesting higher intake of LA may confer metabolic benefit; sources of LA include oils (corn, soybean, and canola), nuts, and seeds. This is consistent with current guidelines for CVD prevention and management that recommend replacement of saturated fats with unsaturated fats, particularly PUFAs.

Acknowledgments

The authors' responsibilities were as follows—VLF: conducted the data analyses; KSP, VKS, VLF, and PMK-E: interpreted the data; KSP: wrote the manuscript; VKS, VLF, FE, MEC, MTB, and PMK-E: critically reviewed the manuscript; and all authors: read and approved the final manuscript.

References

1. Raatz SK, Conrad Z, Jahns L, Belury MA, Picklo MJ. Modeled replacement of traditional soybean and canola oil with high-oleic varieties increases monounsaturated fatty acid and reduces both saturated fatty acid and polyunsaturated fatty acid intake in the US adult population. Am J Clin Nutr 2018;108(3):594–602.
2. Tarrago-Trani MT, Phillips KM, Lemar LE, Holden JM. New and existing oils and fats used in products with reduced trans-fatty acid content. J Am Diet Assoc 2006;106(6):867–80.
3. Sacks FM, Lichtenstein AH, Wu JHY, Appel LJ, Creager MA, Kris-Etherton PM, Miller M, Rimm EB, Rudel LL, Robinson JG, et al. Dietary fats and cardiovascular disease: a presidential advisory from the American Heart Association. Circulation 2017;136(3):e1–23.
4. FDA. Small entity compliance guide: trans fatty acids in nutrition labeling, nutrient content claims, and health claims. (68 FR 41434). [Internet]. 2003 [cited December 11, 2019]. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/small-entity-compliance-guide-trans-fatty-acids-nutrition-labeling-nutrient-content-claims-and#:~:targetText=SUMMARY,supplements.
5. FDA. Final determination regarding partially hydrogenated oils (removing trans fat). [Internet]. [Cited December 11, 2019]. Available from: https://www.fda.gov/food/food-additives-petitions/final-determination-regarding-partially-hydrogenated-oils-removing-trans-fat#:~:targetText=Final Determination Regarding Partially Hydrogenated Oils (Removing Trans Fat),-Share&targetText=In 2015%2C FDA re.
6. Eckel RH, Borra S, Lichtenstein AH, Yin-Piazza SY. Understanding the complexity of trans fatty acid reduction in the American diet: American Heart Association Trans Fat Conference 2006: report of the Trans Fat Conference Planning Group. Circulation 2007;115(16):2231–46.
7. Wu JHY, Marklund M, Imamura F, Tintle N, Korat AVA, De Goede J, Zhou X, Yang W-S, de Oliveira Otto MC, Kröger J. Omega-6 fatty acid biomarkers and incident type 2 diabetes: pooled analysis of individual-level data for 39 740 adults from 20 prospective cohort studies. Lancet Diabetes Endocrinol 2017;5(12):965–74.
8. Marklund M, Wu JHY, Imamura F, Del Gobbo LC, Fretts A, de Goede J, Shi P, Tintle N, Wennberg M, Aslibekyan S. Biomarkers of dietary omega-6 fatty acids and incident cardiovascular disease and mortality: an individual-level pooled analysis of 30 cohort studies. Circulation 2019;139(21):2422–36.
9. Pan A, Chen M, Chowdhury R, Wu JHY, Sun Q, Campos H, Mozaffarian D, Hu FB. α-Linolenic acid and risk of cardiovascular disease: a systematic review and meta-analysis. Am J Clin Nutr 2012;96(6):1262–73.
10. Del Gobbo LC, Imamura F, Aslibekyan S, Marklund M, Virtanen JK, Wennberg M, Yakoob MY, Chiuve SE, Dela Cruz L, Frazier-Wood AC. ω-3 polyunsaturated fatty acid biomarkers and coronary heart disease: pooling project of 19 cohort studies. JAMA Intern Med 2016;176(8):1155–66.
11. Wu JHY, Micha R, Imamura F, Pan A, Biggs ML, Ajaz O, Djousse L, Hu FB, Mozaffarian D. Omega-3 fatty acids and incident type 2 diabetes: a systematic review and meta-analysis. Br J Nutr 2012;107(S2):S214–27.
12. Baylin A, Kim MK, Donovan-Palmer A, Siles X, Dougherty L, Tocco P, Campos H. Fasting whole blood as a biomarker of essential fatty acid intake in epidemiologic studies: comparison with adipose tissue and plasma. Am J Epidemiol 2005;162(4):373–81.
13. Sun Q, Ma J, Campos H, Hankinson SE, Hu FB. Comparison between plasma and erythrocyte fatty acid content as biomarkers of fatty acid intake in US women. Am J Clin Nutr 2007;86(1):74–81.
14. Hodson L, Fielding BA. Stearoyl-CoA desaturase: rogue or innocent bystander? Prog Lipid Res 2013;52(1):15–42.
15. Hodson L, McQuaid SE, Karpe F, Frayn KN, Fielding BA. Differences in partitioning of meal fatty acids into blood lipid fractions: a comparison of linoleate, oleate, and palmitate. Am J Physiol Endocrinol Metab 2009;296(1):E64–71.
16. CDC, National Center for Health Statistics. About the National Health and Nutrition Examination Survey. [Internet]. [Cited March 10, 2020]. Available from: https://www.cdc.gov/nchs/nhanes/about_nhanes.htm.
17. Lagerstedt SA, Hinrichs DR, Batt SM, Magera MJ, Rinaldo P, McConnell JP. Quantitative determination of plasma C8–C26 total fatty acids for the biochemical diagnosis of nutritional and metabolic disorders. Mol Genet Metab 2001;73(1):38–45.
18. CDC, National Center for Health Statistics. 2003–2004 data documentation, codebook, and frequencies: fatty acids–plasma (surplus) (SSFA_C). [Internet]. [Cited March 10, 2020]. Available from: https://wwwn.cdc.gov/Nchs/Nhanes/2003-2004/SSFA_C.htm.
19. CDC, National Center for Health Statistics. 2011–2012 data documentation, codebook, and frequencies: fatty acids–serum (FAS_G). [Internet]. [Cited March 10, 2020]. Available from: https://wwwn.cdc.gov/Nchs/Nhanes/2011-2012/FAS_G.htm.
20. CDC. National Health and Nutrition Examination Survey (NHANES): MEC in-person dietary interviewers procedures manual. [Internet]. CreateSpace Independent Publishing Platform; 2017. Available from: https://www.cdc.gov/nchs/data/nhanes/nhanes_01_02/dietary_year_3.pdf.
21. Ahluwalia N, Dwyer J, Terry A, Moshfegh A, Johnson C. Update on NHANES dietary data: focus on collection, release, analytical considerations, and uses to inform public policy. Adv Nutr 2016;7(1):121–34.
22. Moshfegh AJ, Rhodes DG, Baer DJ, Murayi T, Clemens JC, Rumpler W V, Paul DR, Sebastian RS, Kuczynski KJ, Ingwersen LA. The US Department of Agriculture automated multiple-pass method reduces bias in the collection of energy intakes. Am J Clin Nutr 2008;88(2):324–32.
23. CDC, National Center for Health Statistics . NHANES—National Health and Nutrition Examination Survey homepage. [Internet]. [Cited March 10, 2020]. Available from: https://www.cdc.gov/nchs/nhanes/index.htm.
24. CDC, National Center for Health Statistics . NHANES—National Health and Nutrition Examination Survey–continuous NHANES. [Internet]. [Cited March 20, 2020]. Available from: https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/default.aspx.
25. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28(7):412–9.
26. CDC. Survey methods and analytic guidelines. [Internet]. [Cited March 10, 2020]. Available from: https://wwwn.cdc.gov/nchs/data/nhanes/analyticguidelines/11-12-analytic-guidelines.pdf%0A
27. Harris WS, Mozaffarian D, Rimm E, Kris-Etherton P, Rudel LL, Appel LJ, Engler MM, Engler MB, Sacks F. Omega-6 fatty acids and risk for cardiovascular disease: a science advisory from the American Heart Association Nutrition Subcommittee of the Council on Nutrition, Physical Activity, and Metabolism; Council on Cardiovascular Nursing; and Council on Epidem. Circulation 2009;119(6):902–7.
28. Imamura F, Micha R, Wu JHY, de Oliveira Otto MC, Otite FO, Abioye AI, Mozaffarian D. Effects of saturated fat, polyunsaturated fat, monounsaturated fat, and carbohydrate on glucose-insulin homeostasis: a systematic review and meta-analysis of randomised controlled feeding trials. PLoS Med 2016;13(7):e1002087.
29. Bjermo H, Iggman D, Kullberg J, Dahlman I, Johansson L, Persson L, Berglund J, Pulkki K, Basu S, Uusitupa M, et al. Effects of n-6 PUFAs compared with SFAs on liver fat, lipoproteins, and inflammation in abdominal obesity: a randomized controlled trial. Am J Clin Nutr 2012;95(5):1003–12.
30. Belury MA, Cole RM, Bailey BE, Ke J, Andridge RR, Kiecolt-Glaser JK. Erythrocyte linoleic acid, but not oleic acid, is associated with improvements in body composition in men and women. Mol Nutr Food Res 2016;60(5):1206–12.
31. Hastert TA, de Oliveira Otto MC, Lê-Scherban F, Steffen BT, Steffen LM, Tsai MY, Jacobs DR, Jr, Baylin A. Association of plasma phospholipid polyunsaturated and trans fatty acids with body mass index: results from the Multi-Ethnic Study of Atherosclerosis. Int J Obes 2018;42(3):433.
32. Summers LKM, Fielding BA, Bradshaw HA, Ilic V, Beysen C, Clark ML, Moore NR, Frayn KN. Substituting dietary saturated fat with polyunsaturated fat changes abdominal fat distribution and improves insulin sensitivity. Diabetologia 2002;45(3):369–77.

33. Mensink RP. Effects of saturated fatty acids on serum lipids and lipoproteins: a systematic review and regression analysis. Geneva (Switzerland): WHO; 2016.
34. Maki KC, Lawless AL, Kelley KM, Kaden VN, Geiger CJ, Dicklin MR. Corn oil improves the plasma lipoprotein lipid profile compared with extra-virgin olive oil consumption in men and women with elevated cholesterol: results from a randomized controlled feeding trial. J Clin Lipidol 2015;9(1):49–57.
35. Maki KC, Lawless AL, Kelley KM, Kaden VN, Geiger CJ, Palacios OM, Dicklin MR. Corn oil intake favorably impacts lipoprotein cholesterol, apolipoprotein and lipoprotein particle levels compared with extra-virgin olive oil. Eur J Clin Nutr 2017;71(1):33.
36. Maki KC, Hasse W, Dicklin MR, Bell M, Buggia MA, Cassens ME, Eren F. Corn oil lowers plasma cholesterol compared with coconut oil in adults with above-desirable levels of cholesterol in a randomized crossover trial. J Nutr 2018;148(10):1556–63.
37. Lin L, Allemekinders H, Dansby A, Campbell L, Durance-Tod S, Berger A, Jones PJH. Evidence of health benefits of canola oil. Nutr Rev 2013;71(6):370–85.
38. Schwingshackl L, Bogensberger B, Benčič A, Knüppel S, Boeing H, Hoffmann G. Effects of oils and solid fats on blood lipids: a systematic review and network meta-analysis. J Lipid Res 2018;59(9):1771–82.
39. Rise P, Eligini S, Ghezzi S, Colli S, Galli C. Fatty acid composition of plasma, blood cells and whole blood: relevance for the assessment of the fatty acid status in humans. Prostaglandins, Leukotrienes Essent Fatty Acids 2007;76(6):363–9.
40. de Oliveira Otto MC, Wu JHY, Baylin A, Vaidya D, Rich SS, Tsai MY, Jacobs DR, Jr, Mozaffarian D. Circulating and dietary omega-3 and omega-6 polyunsaturated fatty acids and incidence of CVD in the Multi-Ethnic Study of Atherosclerosis. J Am Heart Assoc 2013;2(6):e000506.
41. Chowdhury R, Warnakula S, Kunutsor S, Crowe F, Ward HA, Johnson L, Franco OH, Butterworth AS, Forouhi NG, Thompson SG, et al. Association of dietary, circulating, and supplement fatty acids with coronary risk: a systematic review and meta-analysis. Ann Intern Med 2014;160(6):398–406.
42. Jovanovski E, Li D, Ho HVT, Djedovic V, Marques ACR, Shishtar E, Mejia SB, Sievenpiper JL, de Souza RJ, Duvnjak L. The effect of α-linolenic acid on glycemic control in individuals with type 2 diabetes: a systematic review and meta-analysis of randomized controlled clinical trials. Medicine (Baltimore) 2017;96(21):e6531.
43. Brenna JT. Efficiency of conversion of α-linolenic acid to long chain n–3 fatty acids in man. Curr Opin Clin Nutr Metab Care 2002;5(2):127–32.
44. Pawlosky RJ, Hibbeln JR, Novotny JA, Salem N. Physiological compartmental analysis of α-linolenic acid metabolism in adult humans. J Lipid Res 2001;42(8):1257–65.
45. Oscarsson J, Hurt-Camejo E. Omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid and their mechanisms of action on apolipoprotein B-containing lipoproteins in humans: a review. Lipids Health Dis 2017;16(1):149.
46. Brown TJ, Brainard J, Song F, Wang X, Abdelhamid A, Hooper L. Omega-3, omega-6, and total dietary polyunsaturated fat for prevention and treatment of type 2 diabetes mellitus: systematic review and meta-analysis of randomised controlled trials. BMJ 2019;366:l4697.
47. Crawford AW, Wang C, Jenkins DJ, Lemke SL. Estimated effect on fatty acid intake of substituting a low-saturated, high-oleic, low-linolenic soybean oil for liquid oils. Nutr Today 2011;46(4):189–96.
48. FDA. Final determination regarding partially hydrogenated oils. [Internet]. 2015 [Cited December 11, 2019]. Available from: https://www.federalregister.gov/documents/2015/06/17/2015-14883/final-determination-regarding-partially-hydrogenated-oils#footnote-1-p34657.