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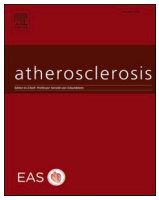

# Dietary *n*-3 alpha-linolenic and *n*-6 linoleic acids modestly lower serum lipoprotein(a) concentration but differentially influence other atherogenic lipoprotein traits: A randomized trial☆

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ABSTRACT

*Background and aims:* Lipoprotein(a) [Lp(a)] is a causal, genetically determined cardiovascular risk factor. Limited evidence suggests that dietary unsaturated fat may increase serum Lp(a) concentration by 10–15 %. Linoleic acid may increase Lp(a) concentration through its endogenous conversion to arachidonic acid, a process regulated by the fatty acid desaturase (*FADS)* gene cluster. We aimed to compare the Lp(a) and other lipoprotein trait-modulating effects of dietary alpha-linolenic (ALA) and linoleic acids (LA). Additionally, we examined whether *FADS1* rs174550 genotype modifies Lp(a) responses.

*Methods:* A genotype-based randomized trial was performed in 118 men homozygous for *FADS1* rs174550 SNP (TT or CC). After a 4-week run-in period, the participants were randomized to 8-week intervention diets enriched with either *Camelina sativa* oil (ALA diet) or sunflower oil (LA diet) 30–50 mL/day based on their BMI. Serum lipid profile was measured at baseline and at the end of the intervention.

*Results:* ALA diet lowered serum Lp(a) concentration by 7.3 % ($p = 0.003$) and LA diet by 9.5 % ($p < 0.001$) ($p = 0.089$ for between-diet difference). Both diets led to greater absolute decreases in individuals with higher baseline Lp(a) concentration ($p < 0.001$). Concentrations of LDL cholesterol (LDL-C), non-HDL-C, remnant-C, and apolipoprotein B were lowered more by the ALA diet ($p < 0.01$). Lipid or lipoprotein responses were not modified by the *FADS1* rs174550 genotype.

*Conclusions:* A considerable increase in either dietary ALA or LA from vegetable oils has a similar Lp(a)-lowering effect, whereas ALA may lower other major atherogenic lipids and lipoproteins to a greater extent than LA. Genetic differences in endogenous PUFA conversion may not influence serum Lp(a) concentration.

## 1. Introduction

Elevated lipoprotein(a) [Lp(a)] is a well-established causal risk factor for cardiovascular diseases (CVD) [1]. Although the plasma concentration of Lp(a) is predominantly determined by genetics (i.e., the *LPA* gene locus), up to 10–30 % of variability in Lp(a) concentrations can be attributed to lifestyle [2]. Indeed, a handful of lifestyle factors, including diet, have been reported to modulate serum Lp(a) concentrations [3,4].

Dietary fatty acids greatly influence CVD risk *via* their effects on serum lipids and lipoproteins [5]. A key strategy in the prevention and management of dyslipidemias is replacing saturated fatty acids (SFA) with unsaturated fatty acids. Recently, there have been concerns that this replacement may lead to a modest 10–15 % increase in Lp(a)

☆ The present study is a secondary analysis of a previously conducted clinical trial (the FADSDIET2 study) which was pre-registered at clinicaltrials.gov as NCT03572205.

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concentration [3,4,6]. However, such studies have increased unsaturated fat intake mostly in the form of monounsaturated fatty acids (MUFA), whereas evidence on polyunsaturated fatty acids (PUFA) is sparse and inconclusive. A few PUFA-enriched intervention diets (from vegetable oils or walnuts) lowered Lp(a) concentration or had no effect [7,8]. The influence of PUFA on Lp(a) is of particular interest, as it has otherwise the most favorable effects on blood lipids [9] and CVD risk [10].

The essential dietary PUFAs alpha-linolenic acid (ALA, 18:3*n*-3) and linoleic acid (LA, 18:2*n*-6) are known to have effects on lipoprotein metabolism distinct from long-chain PUFA [11]. However, to our knowledge, no previous study has successfully isolated their potentially differential effects on Lp(a). Based on cross-sectional data, dietary LA has been hypothesized to increase serum Lp(a) concentration by its endogenous conversion to arachidonic acid (ARA, 20:4*n*-6) [12]. The efficiency of this conversion process is tightly regulated by genetic variation in fatty acid desaturase (*FADS*) gene cluster [13]. Within a previously conducted parallel-arm genotype-based randomized trial [14], we aimed to compare the effects of dietary ALA and LA on serum Lp(a) concentration and to examine the potential moderating role of *FADS1* rs174550 SNP. Based on prior work by Narverud et al. [12], we hypothesized that LA would lead to a higher serum Lp(a) concentration compared to ALA, particularly in carriers of the rs174550-TT genotype, as they exhibit a more efficient conversion of LA to ARA than the CC genotype.

## 2. Patients and methods

### 2.1. Population

A total of 130 Caucasian male participants homozygous for *FADS1* rs174550 SNP (TT or CC) were recruited from the Finnish Metabolic Syndrome in Men (METSIM) cohort [15]. Heterozygous individuals (TC genotype) were excluded because their PUFA metabolism is intermediate to TT and CC and therefore not conducive to detecting diet × genotype interactions. To ensure equal distributions of *FADS1* genotype and other relevant characteristics between the two diet groups, randomization was stratified based on participant's *FADS1* genotype, BMI, age, and fasting plasma glucose concentration. At baseline, the diet groups showed no significant differences in clinical characteristics or serum Lp(a) concentrations (Table 1). Similarly, *FADS1* rs174550-TT and CC genotypes did not differ significantly except for higher serum TG, ApoB, and remnant-C concentrations in the carriers of CC genotype ($p > 0.05$ for each) (Supplementary Table S2). Median Lp(a) concentration in the study population was 15.4 mg/dL and the prevalence of elevated Lp(a) (>50 mg/dL) was 16.1 %.

### 2.2. Intervention

After a 4-week run-in period, the participants were randomized to consume a diet enriched with either *Camelina sativa* oil (ALA diet) or sunflower oil (LA diet) for 8 weeks (Consort flow diagram, Fig. 1). The *Camelina sativa* and sunflower oils contained 57 % and 63 % of PUFA, most of which were ALA and LA, respectively (Supplementary Table S1). The oils were to be consumed unheated at daily doses of 30, 40 or 50 mL for participants within BMI ranges of <24, 24–28 and > 28 kg/m$^2$, respectively. The intervention diets aimed at isocaloric substitution of PUFAs (i.e., ALA or LA) for SFA and MUFA, resulting in unaltered total dietary fat intake. Hence, the participants were instructed to favor low fat and fat free dairy products, lean meat and poultry, and cooking methods that did not require added fat. From the outset of the run-in period to the end of the intervention, the participants abstained from using any oil supplements, including fish oils, and plant sterol or stanol-containing food products. To minimize non-fatty acid-related influences on the primary outcomes, participants were asked to keep physical activity, alcohol intake, smoking, body weight and use of medication unchanged during the study. These factors were measured at baseline and at the end of the intervention by a questionnaire or in the laboratory (weight), and they remained stable over the 8-week intervention period, except for minor weight gain (<1 kg, $p < 0.001$ for both groups, $p = 0.2$ for between-group difference). A total of 12 participants discontinued the intervention, leaving 118 completers for the Lp(a) analyses. Of the completers, 60 followed the ALA diet (TT n = 38, CC n = 22) and 58 followed the LA diet (TT n = 33, CC n = 25). A full description of the study design has been reported previously [14].

**Table 1**
Baseline characteristics of the study participants.

| Characteristics | Overall, N = 118[a] | ALA diet, N = 60[a] | LA diet, N = 58[a] | $p$[b] |
|---|---|---|---|---|
| Age, years | 65.9 (5.6) | 66.3 (5.9) | 65.4 (5.4) | 0.4 |
| Weight, kg | 77.1 (9.4) | 77.6 (10.2) | 76.5 (8.4) | 0.7 |
| Waist circumference, cm[c] | 93.8 (8.2) | 94.8 (9.0) | 92.8 (7.2) | 0.3 |
| Body mass index, kg/m$^2$ | 24.7 (2.6) | 24.7 (2.7) | 24.6 (2.5) | >0.9 |
| Lipoprotein(a), mg/dL | 15.4 (8.1, 37.6) | 17.6 (9.2, 37.6) | 14.4 (7.9, 40.9) | >0.9 |
| Total cholesterol, mmol/L | 5.18 (0.94) | 5.16 (0.95) | 5.20 (0.94) | 0.8 |
| LDL cholesterol, mmol/L | 3.17 (0.86) | 3.15 (0.86) | 3.18 (0.88) | 0.9 |
| True LDL cholesterol, mmol/L | 2.93 (0.91) | 2.94 (0.89) | 2.93 (0.94) | >0.9 |
| Non-HDL cholesterol, mmol/L | 3.56 (0.97) | 3.55 (0.95) | 3.58 (1.00) | 0.7 |
| HDL cholesterol, mmol/L | 1.62 (0.41) | 1.61 (0.36) | 1.62 (0.45) | 0.7 |
| Triglycerides, mmol/L | 1.01 (0.73, 1.25) | 1.04 (0.82, 1.25) | 0.95 (0.70, 1.25) | 0.2 |
| Remnant cholesterol, mmol/L[d] | 1.54 (0.39) | 1.54 (0.40) | 1.54 (0.38) | 0.8 |
| ApoB, g/L[d] | 0.87 (0.20) | 0.88 (0.20) | 0.87 (0.20) | 0.8 |
| ApoA1, g/L[d] | 1.50 (0.21) | 1.49 (0.21) | 1.50 (0.22) | 0.7 |
| ApoB:ApoA1 ratio[d] | 0.60 (0.17) | 0.60 (0.16) | 0.60 (0.17) | 0.9 |
| Fasting plasma glucose, mmol/L | 5.82 (0.43) | 5.83 (0.48) | 5.81 (0.38) | 0.9 |
| C-reactive protein, mg/L | 0.7 (0.3, 1.8) | 0.7 (0.3, 2.0) | 0.8 (0.3, 1.8) | 0.8 |
| Systolic blood pressure, mmHg | 132 (16) | 131 (16) | 133 (16) | 0.7 |
| Diastolic blood pressure, mmHg | 81 (8) | 80 (9) | 82 (7) | 0.3 |
| Current smoker | 8 (6.8 %) | 3 (5.0 %) | 5 (8.6 %) | 0.5 |
| Statin medication | 31 (26 %) | 16 (27 %) | 15 (26 %) | >0.9 |

[a] Mean (SD); Median (1st and 3rd quartiles); n (%).
[b] ALA diet *vs.* LA diet (Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test).
[c] n = 56 for LA diet.
[d] Measured by NMR spectroscopy (n = 57 for LA diet).

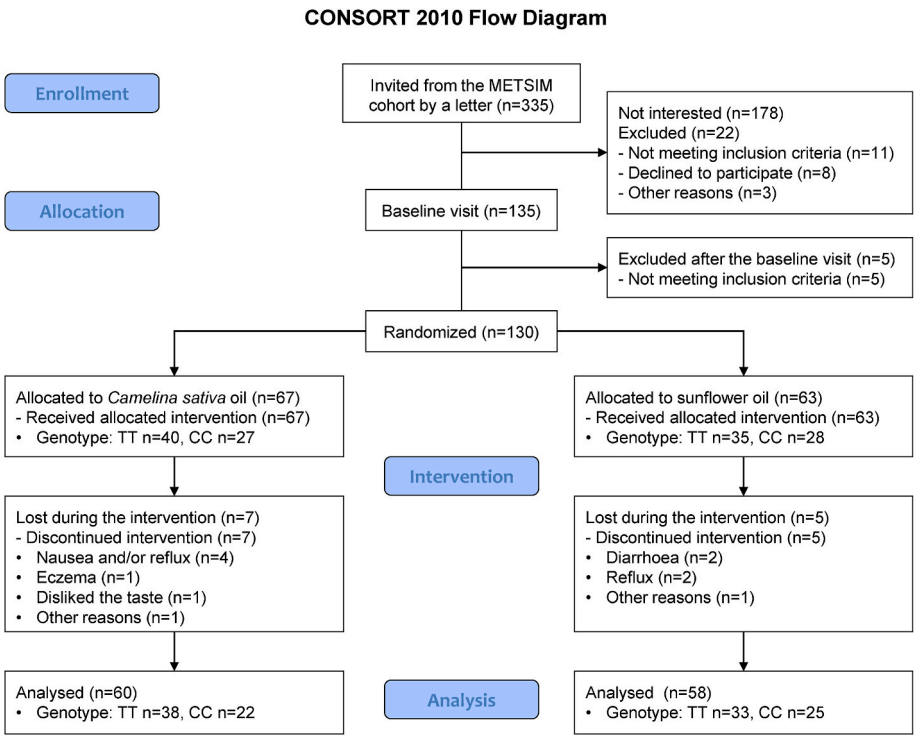


**Fig. 1.** Consort flow diagram.

### 2.3. Ethics approval

The study protocol was approved by the Ethical committee of the Hospital District of Northern Savo (516/2018). Written informed consent was obtained from all participants and the intervention was conducted according to the principles in the Declaration of Helsinki. The study was pre-registered at clinicaltrials.gov as NCT03572205.

### 2.4. Assessment of dietary intake

Dietary intake was assessed using 4-day food records filled on consecutive predefined days including 1 weekend day. Food records were collected at baseline, at 4 weeks, and at the end of the intervention, i.e., at 8 weeks. Portion sizes were weighed or estimated using household measures and portion size pictures. The food records were checked by a clinical nutritionist upon return and analyzed using the AivoDiet nutrient calculation software (v. 2.0.2.1, Aivo Finland, Turku, Finland) based on national and international analyses, and international food composition tables (fineli.fi). In addition to food records, participants were asked to keep a daily log of their oil consumption. Fatty acid composition of plasma phospholipids was used as an objective measure of adherence to the intervention diets.

### 2.5. Laboratory measurements

Fasting plasma samples were collected at baseline and at the end of the 8-week intervention. Lp(a) measurements were performed using a turbidimetric immunoassay (kit 981915, Thermo Fisher Scientific, Vantaa, Finland) and Konelab 20XTi Clinical Chemistry Analyzer. This assay is not affected by apo(a) size heterogeneity. Values that fell below the limit of detection (<5 mg/dL, 16.1 % of all Lp(a) measurements) were imputed assuming a log-normal distribution. Within-run variations (CV%) were 3.4 % and the between-run CV% were 5.5 % for the low serum pool (mean 17.6 mg/dL), 4.2 % for the high pool (mean 118.5 mg/dL), and 2.4 % for total lipid pool (mean 27.8 mg/dL). Serum concentrations of total (TC), low-density (LDL-C) and high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) were measured by enzymatic colorimetric tests (Konelab Systems Reagents). LDL-C corrected for Lp(a) cholesterol (LDL-$C_{corr30}$) was calculated by multiplying Lp(a) mass by 0.30 to derive Lp(a) cholesterol (Lp(a)-C) and then subtracting Lp(a)-C from LDL-C [16]. Remnant-C and apolipoprotein B (ApoB) concentrations were measured by proton nuclear magnetic resonance ($^1$H-NMR) spectroscopy (Nightingale Health Ltd., Helsinki, Finland) [17]. The *FADS1* variant rs174550 was genotyped using the TaqMan SNP Genotyping Assay (Applied Biosystems, Foster City, CA, USA) according to their protocol. Fatty acid composition of plasma phospholipids was analyzed by gas chromatography as previously described [14].

### 2.6. Statistical analyses

Changes in dietary intake and serum lipids, including Lp(a), were analyzed using linear mixed models (R packages lme4 v1.1-30 [18] and lmerTest v3.1-3 [19]). Models were fit using restricted maximum likelihood (REML) method whilst ignoring missing observations. Response variables were Box-Cox transformed to address their generally skewed distributions prior to statistical analyses. Model assumptions were tested by plotting residual and predicted values and by visually inspecting residual Q-Q plots, to test homogeneity of variances and normality of residuals, respectively. Dietary intakes at 4 and 8 weeks were averaged to capture the overall dietary exposure during the intervention. Within the diet groups, mixed models were run using the dietary factor or lipid trait of interest as the response variable, subject identifier as a random effect (intercept) and timepoint, *FADS1* genotype, and genotype × timepoint interaction as fixed effects. The genotype × timepoint interaction term was used to determine whether the *FADS1* genotype (TT *vs.* CC) modified changes in Lp(a) or other lipoprotein traits. To compare changes between the diets (i.e., diet × timepoint interaction), data from both ALA and LA diet groups were pooled together and similar models were run using timepoint, diet, *FADS1* genotype, and all combinations of their interactions as fixed effects. For alcohol intake, a generalized mixed model was used instead due to extreme skewness. The influence

of baseline Lp(a) concentration on 8-week changes in Lp(a) was analyzed using linear regression with quartiles of baseline Lp(a) concentration as the independent variable. For each quartile, baseline and 8-week values were compared using the paired samples Wilcoxon signed-rank test. The influence of baseline values on the changes in serum lipid profile was also tested using Spearman rank correlation coefficient. Data are presented as mean (SD), median (IQR) or n (%) in tables and as mean (95 % confidence interval) in figures. Percentage (%) changes from baseline were summarized as medians due to heavily right-skewed distributions. Baseline characteristics were compared between the diet groups and genotypes using the Wilcoxon signed-rank test, Pearson's Chi-squared test, or Fisher's exact test. The power calculation of the trial was based on the change in ARA proportion (mol-%) in cholesteryl esters in response to a high-LA diet observed in our previous trial [20]. All statistical analyses were performed using R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria). All tests were two-tailed and $p$ values $< 0.05$ were considered statistically significant.

## 3. Results

### 3.1. Dietary intake

Both diets resulted in a 2-fold increase in total PUFA intake (Fig. 2A, Supplementary Table S3). The increase was mostly ALA (+13.0 g/d, 6-fold increase) on the ALA diet and LA (+20.6 g/d, 3-fold increase) on the LA diet. Consequently, dietary LA:ALA ratio decreased from 4:1 to 1:1 on the ALA diet and increased to 13:1 on the LA diet. The increase in PUFA came at the expense of some SFA, carbohydrates and protein. The slight decrease in SFA proportion was equal on both diets, whereas MUFA proportion increased slightly more on the ALA diet ($p = 0.045$ for between-diet difference). Increased total energy intake (+156 and +162 kcal/d) had a minor effect on participants' body weight (+0.7 and +0.9 kg on ALA and LA diets, respectively, $p < 0.01$ for each). Other dietary factors known to influence serum lipid profile (fiber, cholesterol, marine $n$-3 PUFA [EPA and DHA], and alcohol), remained unchanged during the intervention ($p > 0.05$ for each). The ALA and LA diets led to distinct changes in plasma phospholipid ALA, LA, and ARA proportions (mol-%) ($p < 0.001$ for between-diet differences) (Fig. 2B). The effect of the LA diet on phospholipid LA and ARA proportions was modified by the *FADS1* genotype. LA tended to cumulate in phospholipids more in the CC genotype (i.e., 'poor' converters) than in TT individuals ($p = 0.010$ for between-genotype difference). Notably, phospholipid ARA proportion decreased in the CC genotype, whereas it remained unchanged in the TT genotype ($p < 0.001$ for between-genotype difference).

### 3.2. Serum total and lipoprotein lipids

Serum Lp(a) concentration decreased by 7.3 % on the ALA diet ($p = 0.003$) and 9.5 % on the LA diet ($p < 0.001$) during the 8-week intervention period (Fig. 3, Table 2). These changes occurred similarly on both diets ($p$=0.089 for between-diet difference) and were not modified by the *FADS1* rs174550 genotype ($p > 0.5$ for between-genotype differences).

Change in Lp(a) concentration was then examined by quartiles of baseline Lp(a) concentration, as individuals with low concentrations would not be expected to have clinically relevant changes in response to diet (Fig. 4). On both diets, participants with higher baseline Lp(a) showed a greater decrease in Lp(a) concentration over the 8-week intervention ($p < 0.001$ for linear trends). In the highest quartile of baseline Lp(a), the mean changes were −7.0 (SD 8.4) mg/dL ($p = 0.007$) and −6.7 (7.9) mg/dL ($p = 0.003$) for the ALA and LA diets, respectively ($p = 0.74$ for the between-diet difference). Baseline Lp(a) concentration as a continuous variable was also correlated with 8-week changes in Lp(a) concentration (ALA diet: rho = −0.44, LA diet: rho = −0.46, $p < 0.001$ for both diets). Additionally, we investigated cross-sectional correlations between plasma phospholipid fatty acid proportions and Lp(a) concentration at baseline. Plasma phospholipid LA was inversely associated with Lp(a) concentration in Spearman correlation analysis (rho = −0.22, $p = 0.016$), whereas other phospholipid PUFAs were not

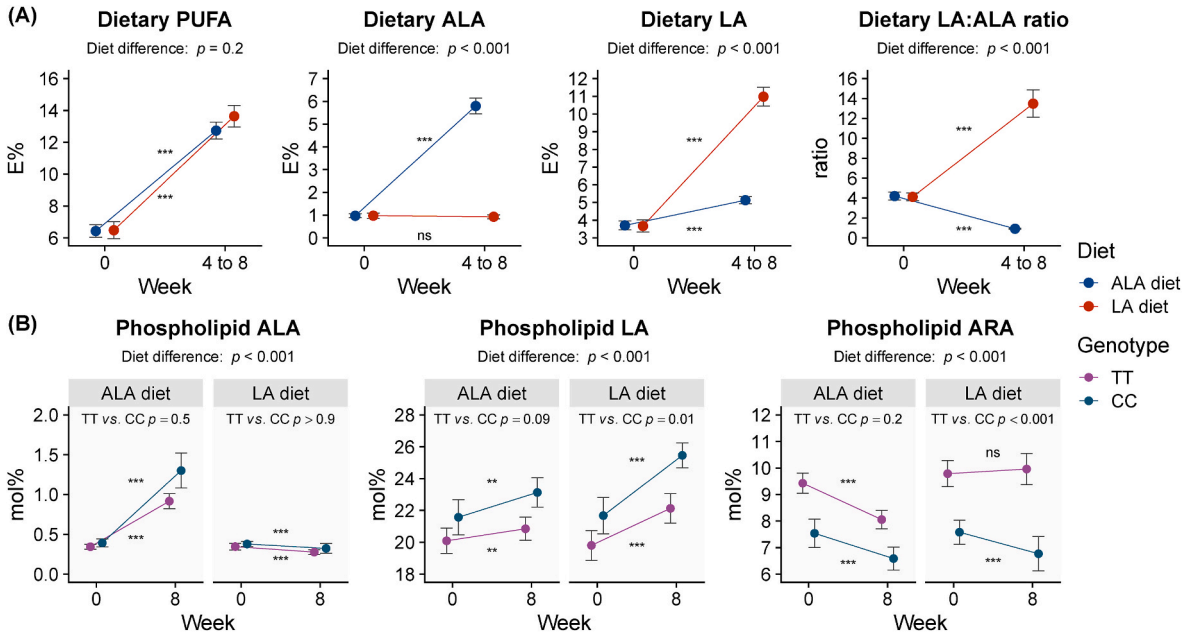


**Fig. 2.** Changes in dietary PUFA intake and corresponding plasma biomarkers.
(A) Dietary intakes of polyunsaturated fatty acids (PUFA), alpha-linolenic acid (ALA), linoleic acid (LA), and LA:ALA ratio based on 4-day food records. Lines and error bars indicate means and their 95 % confidence intervals. Blue and red dots and lines stand for ALA and LA diets, respectively. (B) Plasma phospholipid ALA, LA, and arachidonic acid (ARA) proportions stratified by the *FADS1* rs174550 genotype. Purple and turquoise dots and lines stand for TT and CC genotypes, respectively. *P* values for between-diet differences (i.e., diet × time interaction) are shown above each plot. *p*-values for within-group changes are shown beside the lines as *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. TT *vs.* CC stands for comparison of changes between genotypes (genotype × time interaction). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

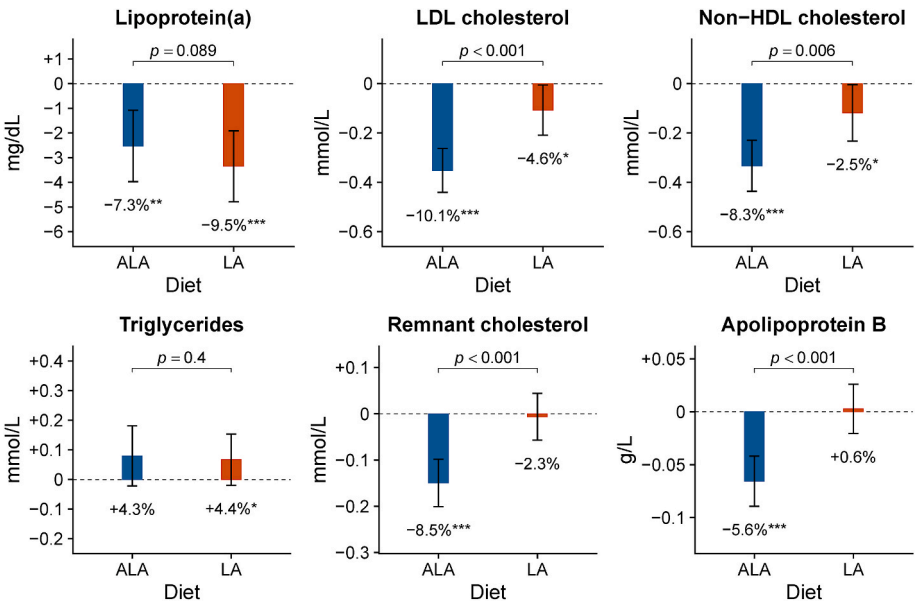


**Fig. 3.** Changes in serum lipoprotein(a), LDL cholesterol, non-HDL cholesterol, triglycerides, remnant cholesterol, and apolipoprotein B concentrations over the 8-week intervention.
Points and error bars stand for mean changes and their 95 % confidence intervals, respectively. *p* values for between-diet differences (i.e., diet × time interaction) are shown at the top of each plot. *p*-values for within-group changes are given after median percent changes as $*p < 0.05$, $**p < 0.01$, $***p < 0.001$.

**Table 2**
Changes in serum lipoprotein(a) concentration and other lipoprotein traits.

| | ALA diet (N = 60) | | | LA diet (N = 58) | | | |
|---|---|---|---|---|---|---|---|
| Lipid trait | Change[a] | $p_{time}$[b] | $p_{time\times genotype}$[c] | Change[a] | $p_{time}$[b] | $p_{time\times genotype}$[c] | $p_{time\times diet}$[d] |
| Lipoprotein(a), mg/dL | −2.53 (5.60) | **0.003** | 0.8 | −3.35 (5.48) | **<0.001** | 0.6 | 0.089 |
| Total cholesterol, mmol/L | −0.30 (0.39) | **<0.001** | 0.4 | −0.12 (0.47) | **0.043** | 0.6 | **0.023** |
| LDL cholesterol, mmol/L | −0.35 (0.34) | **<0.001** | 0.2 | −0.11 (0.39) | **0.035** | 0.7 | **<0.001** |
| LDL cholesterol$_{corr30}$, mmol/L | −0.33 (0.35) | **<0.001** | 0.2 | −0.08 (0.39) | 0.11 | 0.8 | **<0.001** |
| Non-HDL cholesterol, mmol/L | −0.33 (0.40) | **<0.001** | 0.4 | −0.12 (0.43) | **0.031** | 0.3 | **0.006** |
| HDL cholesterol, mmol/L | +0.03 (0.21) | 0.4 | 0.8 | −0.00 (0.17) | 0.9 | 0.3 | 0.6 |
| Triglycerides, mmol/L | +0.08 (0.39) | 0.4 | 0.3 | +0.07 (0.33) | **0.025** | 0.14 | 0.4 |
| Remnant cholesterol, mmol/L[e] | −0.15 (0.20) | **<0.001** | 0.083 | −0.01 (0.19) | 0.7 | 0.4 | **<0.001** |
| ApoB, g/L[e] | −0.07 (0.09) | **<0.001** | 0.2 | +0.00 (0.09) | >0.9 | 0.15 | **<0.001** |
| ApoA1, g/L[e] | +0.01 (0.11) | 0.9 | 0.7 | −0.00 (0.11) | >0.9 | 0.4 | >0.9 |
| ApoB:ApoA1 ratio[e] | −0.04 (0.07) | **<0.001** | 0.5 | +0.00 (0.06) | >0.9 | 0.064 | **<0.001** |

[a] Mean (SD).
[b] Change from baseline within diet group.
[c] Difference between genotypes within diet group.
[d] Difference between diet groups.
[e] Measured by NMR spectroscopy (n = 57 for LA diet at baseline).

associated with Lp(a) concentration.

Both diets lowered serum LDL-C (ALA –10.1 %, $p < 0.001$ *vs.* LA –4.6 %, $p = 0.035$), non-HDL-C (ALA –8.3 %, $p < 0.001$ *vs.* LA –2.5 %, $p = 0.031$), and TC (ALA –5.4 %, $p < 0.001$. *vs.* LA –0.7 %, $p = 0.043$) concentrations, but these changes were more pronounced on the ALA diet ($p < 0.05$ for between-diet differences) (Fig. 3). After correcting LDL-C for cholesterol contained by Lp(a) (i.e., LDL-C$_{corr30}$), the change remained significant on the ALA diet (−10.3 %, $p < 0.001$) but not on the LA diet (−3.3 %, $p = 0.110$). Although mean changes in Lp(a) and LDL-C concentrations were concordant, these did not correlate on individual level on ALA (rho = −0.07, $p = 0.6$) or LA diet (rho = 0.18, $p = 0.2$). Only ALA diet lowered remnant-C (−8.5 %, $p < 0.001$), which reflects cholesterol carried by VLDL and IDL particles (between-diet difference $p < 0.001$). ApoB concentration, which captures all atherogenic lipoprotein particles, decreased only on the ALA diet (−5.6 %, $p < 0.001$), whereas no change was observed on the LA diet (+0.6 %, $p > 0.9$, between-diet difference $p < 0.001$). Concentration of serum TGs increased slightly on the LA diet (+4.4 %, $p = 0.025$), whereas HDL-C concentration remained unchanged on both diets ($p > 0.5$). None of these changes were modified by the *FADS1* genotype ($p > 0.05$ for all genotype × time interactions).

## 4. Discussion

The novel findings of this genotype-based randomized trial are the 7–10 % decrease in serum Lp(a) concentration on both ALA or LA-enriched diets, as well as a divergent effect of these essential PUFAs on major atherogenic lipoprotein traits, such as LDL-C, non-HDL-C, remnant-C and ApoB (Fig. 5). The *FADS1* rs174550 genotype did not modulate Lp(a) responses to diets, and thus our results do not support the role of endogenous LA to ARA conversion in the regulation of Lp(a) concentration.

The observed decrease in Lp(a) concentration following PUFA-enriched diets appears to conflict with previous findings that have suggested an Lp(a)-increasing role for dietary unsaturated fat. This seeming contradiction might be resolved by the quality of dietary

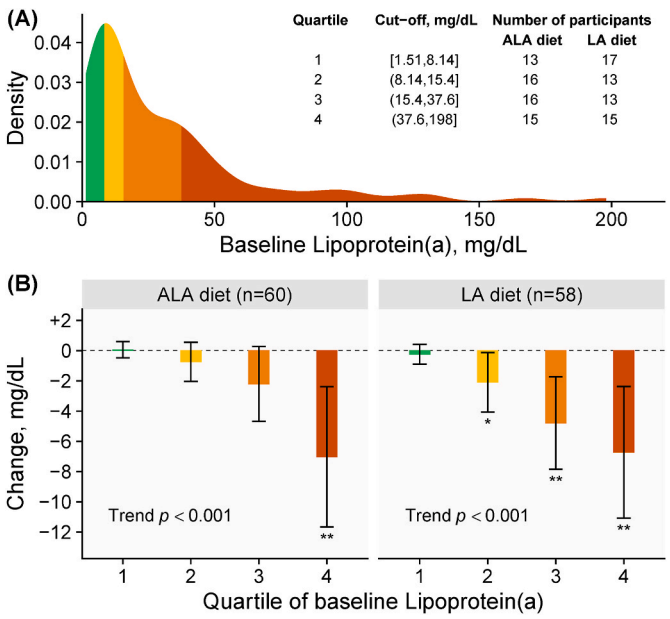


**Fig. 4.** The influence of baseline Lp(a) concentration on 8-week changes.
(A) Baseline distribution of Lp(a). (B) Changes in serum Lp(a) concentration by quartiles of baseline Lp(a) concentration. Columns and error bars indicate means and 95 % confidence intervals. Trend *p* values stand for linear trends across quartiles. For each quartile, change from baseline was tested using paired samples Wilcoxon signed-rank test, *p*-values for which are denoted as $*p < 0.05$, $**p < 0.01$, $***p < 0.001$.

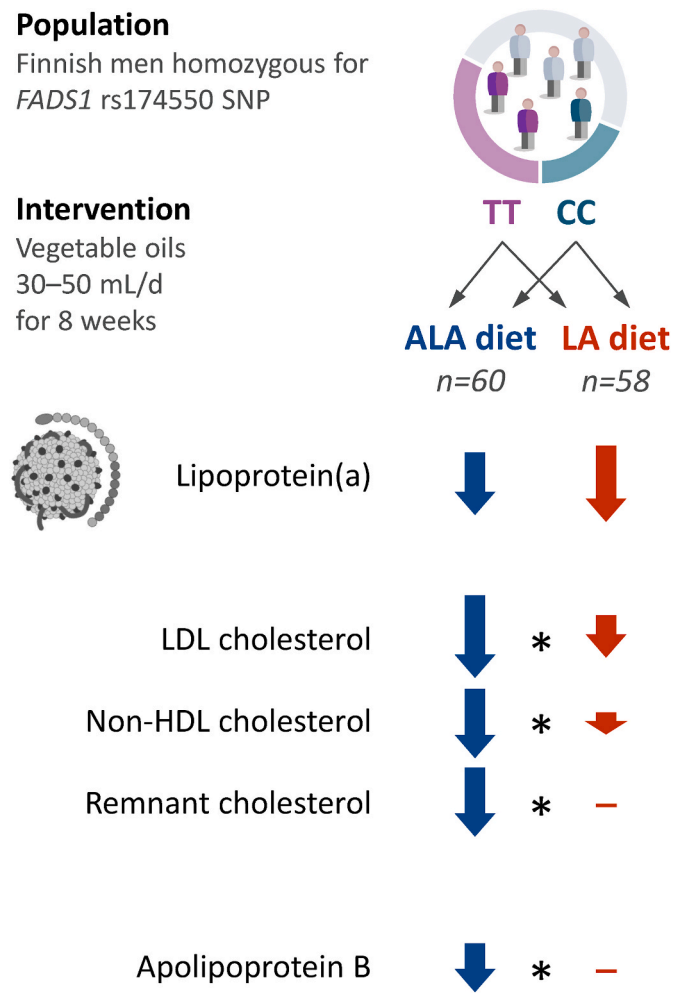


**Fig. 5.** Both dietary alpha-linolenic acid (ALA) and linoleic acid (LA) modestly lower serum lipoprotein(a) concentration, but ALA shows more beneficial effects on other major atherogenic lipoprotein traits.
Changes in lipoprotein(a) are not modified by the *FADS1* rs174550 SNP. $*p <$ 0.05 for between-diet difference.

unsaturated fat, which has in most prior studies been dominated by MUFA instead of PUFA [21–24]. Divergent changes in Lp(a) and LDL-C concentrations also occurred when intakes of both MUFA and PUFA were simultaneously increased, such as in a Norwegian study in female students [25] and a Swedish study in hyperlipidemic subjects [26]. An increase in Lp(a) concentration was also found by a UK study that attempted to compare *n*-3 and *n*-6 PUFA-enriched diets against a high-SFA diet. In this study, however, both diets were enriched with olive oil, a major source of MUFA, and the *n*-3 PUFA originated from fish oil instead of plant sources [27]. The evidence on essential PUFAs and Lp(a) is sparse and inconsistent, as a few PUFA-enriched (with vegetable oils or walnuts) intervention diets produced no change [24] or a decrease in Lp(a) [8]. Compatible with our findings, Tindall et al. (2020) observed an 11.5 % decrease in serum Lp(a) on a diet high in both *n*-3 and *n*-6 PUFA from flaxseed oil and high-LA safflower oil [7]. Interestingly, this Lp(a)-lowering effect was not shared by a walnut-enriched diet despite a matched fatty acid composition. The present study brings clarity to the conflicting evidence by comparing two oils (*Camelina sativa* and sunflower) that are equally rich in PUFA but possess extreme ALA and LA contents, respectively.

In the current study, the LA-enriched diet produced a 9.5 % decrease in serum Lp(a) concentration, which contradicts our hypothesis and those proposed by others [12]. Narverud et al. (2019) found a novel association between plasma ARA proportion and Lp(a) in subjects with familial hypercholesterolemia and speculated that dietary LA would increase serum Lp(a) concentration *via* its endogenous conversion to ARA [12]. Our study directly opposes this hypothesis by showing that a considerable increase in dietary LA intake does not increase plasma phospholipid ARA proportion even in the rs174550-TT genotype (i.e., 'efficient' converters). Indeed, this lack of LA-induced increase in ARA proportions of different lipid pools, such as erythrocyte membranes or plasma/serum phospholipids has been demonstrated in multiple RCTs [28], including ours [14]. Furthermore, in the present study, the LA-enriched diet produced a decrease in Lp(a), instead of the hypothesized increase. No cross-sectional relationship was found between phospholipid ARA proportion and Lp(a) concentration. Instead, higher plasma phospholipid LA proportion was associated with lower serum Lp(a) concentration, further supporting the Lp(a)-lowering role of LA. Although the present study does not support the role of endogenous long-chain PUFA synthesis in the dietary regulation of Lp(a), we acknowledge that such phenomenon could still exist (or be more easily detectable) in familial hypercholesterolemia [12].

The clinical significance of the present diet-induced changes in Lp(a) is uncertain. According to Mendelian randomization studies, large absolute reductions of 50–100 mg/dL [29–31] in Lp(a) would be required to lower CVD risk by 20 %. Like most studies on diet and Lp(a), ours was a secondary analysis of a trial that did not pre-select individuals based on their Lp(a) concentration. However, participants with higher baseline Lp(a) showed significantly greater absolute decreases in serum Lp(a) concentrations (~−7 mg/dL in the highest quartile). Based on the Mendelian studies, this would reduce relative CVD risk by approximately 1–3%. For comparison, the mean changes in LDL-C concentration observed on the ALA (−0.35 mmol/L) and LA diets (−0.11 mmol/L) would translate to relative CVD risk reductions of 8 % and 2 %, respectively [32]. Although the modest improvement in Lp(a) is likely of minor clinical significance, our results may help alleviate current concerns related to recommending these PUFAs for the ~20 % [33] of the global population suffering from elevated Lp(a) [6].

The ALA-enriched diet was found to lower serum LDL-C, non-HDL-C

and TC concentrations to a greater extent than the LA diet. Furthermore, only the ALA-enriched diet lowered ApoB and Remnant-C. This is a novel finding, as previous trials have reported similar effects of ALA and LA on serum lipid profile [34,35]. Neither isocaloric substitution of ALA for LA [36,37] or manipulating ALA:LA ratio have altered serum lipoprotein profile [38]. Similarly, a network meta-analysis found no difference between the LDL-C-modulating effects of sunflower and flaxseed oils, although the number of studies was small [39]. The current study directs attention to potentially distinct lipoprotein-modulating effects of ALA and LA, which have often been pooled together in studies on dietary fat and blood lipids [9]. Further studies are warranted on whether the antihyperlipidemic effects of LA are indeed weaker compared to ALA. It is well known that current clinical measurements of LDL-C include cholesterol carried by Lp(a) particles (i.e., Lp(a)-C). In the present study, removing overlapping Lp(a)-C from LDL-C rendered the change in LDL-$C_{corr30}$ (LDL-C corrected for Lp(a)-C) non-significant on the LA diet. This implies that the modest effect of LA on LDL-C is partly driven by LA's influence on Lp(a) concentration.

The mechanisms that could explain the decrease in Lp(a) concentration are largely unknown. It is more likely that dietary fatty acids influence Lp(a) *via* hepatic apo(a) synthesis rather than catabolism of Lp(a), as the role of LDL receptor in Lp(a) homeostasis is uncertain [3]. In the present study, the LA diet lowered Lp(a) concentration but not that of ApoB. This suggests that less apo(a) were bound to LDL, but these lipoproteins were nevertheless released into the circulation as LDL. As some apo(a) can also bind to VLDL and IDL particles (i.e., triglyceride-rich lipoproteins, TRL) [40], it is plausible that the remnant-C-lowering effect of ALA could decrease the likelihood of apo(a) binding to TRLs. On the other hand, apo(a)-TRLs have been positively associated with serum TGs, which increased slightly on the LA diet. Although the focus in dietary fat quality is typically on the degree of unsaturation, it has also been suggested that the effect of dietary fatty acids on Lp(a) concentration may depend on fatty acid chain length rather than unsaturation degree, with longer chain length increasing Lp(a) [4]. Our results neither support nor contradict this hypothesis, as the comparators (ALA and LA) both include 18 carbon atoms and their effects on Lp(a) appear very similar.

Major strengths of our study include its genotype-based randomized design and good adherence to the oil supplementation regimen. Owing to the homogeneous study population, we were able to demonstrate that aging Eastern Finnish men have a remarkably high median Lp(a) concentration (15.4 mg/dL) for a Finnish population. As for comparison, using a similar assay, a large population-based study reported a median of 4.6 mg/dL for Finns [41]. Inclusion of males only could also be seen as a strength, as females experience a selective increase in Lp(a) around the menopause [42]. The duration of the intervention period (8 weeks) was longer than in most previous studies (3–8 weeks) [3]. This is ample for serum lipid profile to reach a new steady state, as shown by previous studies demonstrating stability in Lp(a) and other lipoprotein lipid concentrations within intervention weeks 5–7 [22], or 5–8 [21]. In the present study, the 8-week intervention diets led to clear genotype-specific alterations in plasma phospholipid composition, affirming that our hypothesis regarding the influence of long-chain PUFA conversion on Lp(a) concentration was successfully tested. Despite the long duration, the study exhibited good adherence, with low drop-out rates of 10.4 % and 7.9 % on the ALA and LA diets, respectively, suggesting that such an intervention could be feasible long-term.

A limitation of our study is that the isocaloric substitution of PUFA for SFA and MUFA was not quite achieved. The direction of change in Lp(a) concentration is very likely influenced not only by increased PUFA intake but also by the background diet (particularly whether SFA intake decreases or not). In our study, SFA proportion decreased slightly but significantly, and this reduction was equal on both diets. More drastic SFA reduction in prior studies can partly explain the contradiction between the present Lp(a)-lowering effect and previously often reported diet-induced increases in Lp(a)-concentration. The most prominent dietary change in the present study was the substantial increase in PUFA intake (ALA or LA depending on the diet). Both diets led to a similar, modest increase in total dietary fat and energy intake, as well as minor weight gain (<1 kg). This is unlikely to explain the observed decrease in Lp(a), since even substantial changes in body weight do not appear to independently influence Lp(a) [43]. However, positive energy balance could explain the slight tendency towards increased serum TG concentration [44]. Indeed, serum TGs should be lowered by a successful isocaloric increase in PUFA intake (mainly LA plus ALA) [9]. It is worth noting that non-fatty acid components present in the *Camelina sativa* and sunflower oils could have contributed to the observed changes in serum lipids and lipoproteins. The trial was originally designed to provide 80 % power for detecting changes in plasma fatty acid composition – although this secondary analysis showed significant decreases in Lp(a) concentration (i.e., main effect of time), the study might have been underpowered to detect differences between diets or genotypes. Lastly, our study population was limited to middle-aged and older Caucasian males, and as such, our findings may not be generalizable to younger individuals, females, other ethnicities, and individuals heterozygous for *FADS1* rs174550 SNP.

In conclusion, a substantial increase in dietary intake of either ALA or LA from vegetable oils has a similar, favorable effect on serum Lp(a) concentration. The modest decrease in Lp(a) is more apparent in individuals with high baseline Lp(a) levels. ALA appears to decrease LDL-C, non-HDL-C, remnant-C and ApoB more effectively than LA. The PUFA-induced Lp(a)-lowering effects are not modified by the *FADS1* rs174550 genotype, suggesting that endogenous long-chain PUFA conversion may not play a role in regulating serum Lp(a) concentration.

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## Data availability

Individual participant data are not available because of sensitive genetic information and because we do not have permission by the ethical committee nor the consent by the participants for the data to be made available.

## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Petrus Nuotio reports a relationship with Nightingale Health Ltd. that includes: equity or stocks. Topi Meuronen reports a relationship with Afekta Technologies Ltd. that includes: consulting or advisory, employment, and paid expert testimony. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## CRediT authorship contribution statement

**Petrus Nuotio:** Conceptualization, Software, Formal analysis, Writing – original draft, Visualization, Funding acquisition. **Maria A. Lankinen:** Conceptualization, Methodology, Investigation, Writing – original draft, Supervision, Project administration, Funding acquisition. **Topi Meuronen:** Investigation, Writing – review & editing. **Vanessa D. de Mello:** Conceptualization, Investigation, Data curation, Writing –

review & editing. **Taisa Sallinen:** Investigation, Writing – review & editing. **Kirsi A. Virtanen:** Investigation, Writing – review & editing. **Jussi Pihlajamäki:** Conceptualization, Writing – review & editing, Supervision. **Markku Laakso:** Resources, Writing – review & editing, Funding acquisition. **Ursula Schwab:** Conceptualization, Methodology, Investigation, Writing – original draft, Supervision, Project administration, Funding acquisition.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2024.117562.

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